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ARTMENTS OF LABOR AND HEALTH, EDUCATION, AND WELFARE APPROPRIATIONS FOR 1963

HEARINGS

BEFORE A

SUBCOMMITTEE OF THE
COMMITTEE ON APPROPRIATIONS
HOUSE OF REPRESENTATIVES

EIGHTY-SEVENTH CONGRESS

SECOND SESSION

SUBCOMMITTEE ON DEPARTMENTS OF LABOR AND HEALTH, EDUCATION, AND WELFARE AND RELATED AGENCIES APPROPRIATIONS

JOHN E. FOGARTY, Rhode Island, *Chairman*

WINFIELD K. DENTON, Indiana
FRED MARSHALL, Minnesota
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ROBERT H. MICHEL, Illinois

ROBERT M. MOYER, *Staff Assistant to Subcommittee*

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

PART 3

Public Health Service

(National Institutes of Health)

Printed for the use of the Committee on Appropriations

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DEPARTMENTS OF LABOR AND HEALTH, EDUCATION, AND WELFARE APPROPRIATIONS FOR 1963

NATIONAL INSTITUTES OF HEALTH

Wednesday, February 7, 1962.

WITNESSES

DR. JAMES A. SHANNON, DIRECTOR
DR. DAVID E. PRICE, DEPUTY DIRECTOR
DR. G. BURROUGHS MIDER, DIRECTOR OF LABORATORIES AND CLINICS
DR. HALSEY HUNT, CHIEF, DIVISION OF GENERAL MEDICAL SCIENCES
DR. SEYMOUR J. KRESHOVER, ACTING DIRECTOR, NATIONAL INSTITUTE OF DENTAL RESEARCH
RICHARD L. SEGGEL, EXECUTIVE OFFICER
JOSEPH S. MURTAUGH, CHIEF, OFFICE OF PROGRAM PLANNING
DR. LUTHER L. TERRY, SURGEON GENERAL
JAMES F. KELLY, DEPARTMENT BUDGET OFFICER

Mr. Fogarty. Dr. Shannon, we are ready now for your opening statement on the National Institutes of Health.

General Statement

Dr. Shannon. Mr. Chairman and members of the committee, I am very happy to be able to report to you that, since the last time I appeared before this committee, there have been very significant forward strides both in the substance of biomedical research and in the further development of effective NIH grant support programs for this vitally important work. When the committee examines the record of this past year, I am confident that it will find ample justification for its faith in this country's scientists and research institutions and for its firm support of their efforts.

ACHIEVEMENTS OF NIH

With your permission, Mr. Chairman, I should first like to discuss briefly the substantive progress that has been made in our understanding of disease and of the biological processes on which health depends. It is to this end that all NIH programs—and the congressional appropriations which make them possible—are directed. It is in terms of scientific progress, on the one hand, and the unsolved problems that remain, on the other, that the effectiveness of existing programs and the need for their continuance or expansion must be judged.

ADVANCE IN GENETICS

Two recent achievements by NIH scientists deserve special mention. One of these has been described by the press as "the partial cracking of the genetic code." Briefly, what has happened is that a stable laboratory system has been developed for synthesizing proteins from amino acids (as is done by all living cells) in a way that throws light on the role of individual nucleic acids in this synthesizing process. The evidence suggests that a particular type of nucleic acid will cause the system to select a particular amino acid, from the 20 or more available, for the synthesis of specific proteins. This is the first step toward cataloging the effects of nucleic acids which are believed to be the means by which hereditary characteristics are transmitted. An understanding of this process will lay the foundation for a whole series of developments that may some day give man control over a host of congenital disabilities and predispositions to disease.

IDENTIFICATION OF AN IMPORTANT CAUSE OF PNEUMONIA

Another very important development is that a member of an obscure group of microbes, known as pleuropneumonia-like organisms or PPLO, has for the first time been identified as an important cause of pneumonia. This so-called Eaton agent, which was discovered in 1944, is the first PPLO shown to be responsible for a disease in man. The method for growing this PPLO will permit the specific diagnosis of a common form of pneumonia and facilitate the development of a vaccine. However, the long-range importance of this work, which was done by two NIH scientists and a member of the Wistar Institute in Philadelphia, is that a whole group of organisms not hitherto known to cause human disease is now suspect.

In a statement which must deal with several major aspects of NIH activity, it is, of course, impossible to survey all the many facets of biomedical research. The report on the highlights of research, which has already been submitted to the committee, describes several hundred significant contributions which have been added to the record of achievement during the past year. I cannot say with certainty which of these items will be recognized 2, 5, or 10 years from now as having made the greatest contribution to the welfare of mankind—without the benefit of hindsight it is impossible to make a final evaluation of a piece of research. The further pursuit of some startling new discoveries will probably lead us up blind alleys while some observation, of little immediate interest and of no apparent relevance to any particular problem, may well turn out to be the first step in a fruitful line of research and may ultimately be regarded as having been a major breakthrough. Such is the nature of research, especially in the biological sciences which still lack a comprehensive theoretical basis and in which most research must, necessarily, continue to be empirical and many advances will be fortuitous. This fluidity of the biological sciences is a strong argument, Mr. Chairman, for maintaining a broad national research effort. Only by continuing to press forward on all the fronts that hold any promise of success can we hope to conquer the dread diseases to which man falls victim.

I shall, therefore, not attempt to catalog what seems to be the most outstanding research results of the past year. Specific examples of progress in many fields will be presented in the testimony of the Institute directors. I should, however, like to take a few minutes to describe, by way of example, the progress, the opportunities, and the problems in two broad fields, each of which, in its own way, is at a turning point: virology and research in atherosclerosis.

VIROLOGY AND THE NEED FOR BASIC RESEARCH

Viral research is a field which has seen major achievements during the past few years and in which dramatic further advances seem to lie just over the horizon. The accelerated pace of research in this field is largely due to improved laboratory techniques which, at the time of their development, were far removed from any clinical problem. More readily controllable and simpler tissue culture methods have facilitated the isolation and cultivation of viruses and the production of vaccines. More refined use of the electron microscope has made it easier to identify viruses. More sophisticated immunological methods have made it possible to relate specific viruses to specific diseases.

One happy result of these technical advances was the Salk polio vaccine which has already had a crushing effect on the prevalence of this tragic disease. Oral vaccines for two of the three types of polio were licensed for production during the past year. These oral vaccines, made from attenuated live viruses, are more easily administered and will provide immunity more rapidly.

DEVELOPMENT OF AN EFFECTIVE MEASLES VACCINE

We may look forward, in the not too distant future, to an effective measles vaccine. A number of trials by various investigators have already been completed. Members of the staff of the Division of Biologics Standards are already conducting a large-scale pilot study of a live virus vaccine in west Africa, where measles is accompanied by a very high death rate. At the same time, the Communicable Disease Center in Atlanta has arranged trials in five metropolitan areas in this country of a killed virus vaccine and a mixed course of injections using both vaccines. Initial production of the vaccine and the development of standards of safety and potency are underway.

Although measles is usually a fairly mild disease in this country, because general health and nutritional standards and clinical care of the disease are good, it is actually responsible for more deaths than poliomyelitis and may lead to encephalitis, with resultant mental retardation, to deafness, or to other complications. A practical measles vaccine will therefore be a welcome addition to the physician's armamentarium.

The development of the measles vaccine provides a good example of the complexities of medical research and the amount of work that must precede the clinical application of a so-called breakthrough. It was first suspected that measles was a virus disease as long ago as 1905 and this fact was pretty well established by 1930. But the techniques then available did not make it possible to identify the virus. It was finally isolated in 1954 and since then intensive work, involving a number of conferences called by NIH to resolve various developmental and clinical problems, has led to the two vaccines that are now being tested. To move from the first isolation of a virus to field tests of two vaccines in 7 years is rapid progress, Mr. Chairman, and it illustrates why medical research must have long-term support to yield the results of which it is capable.

PROGRESS IN COMBATING RESPIRATORY DISEASE

Great strides are now being made in the attack on acute respiratory diseases which are a leading cause of death among infants and are responsible for more temporary disability among adults than any other factor—the population as a whole averages 1.2 respiratory illnesses per year. Well over half of these illnesses are believed to be due to viruses. Some 30 or 40 respiratory viruses have already been identified and many more are suspected. A very important development of the past year was the discovery that one of these viruses is responsible for a major portion of severe respiratory disease in young children and for a significant amount of milder adult illnesses. This holds out the hope that a single vaccine may be developed which will effectively reduce the incidence of respiratory illness, especially among children.

CANCER RESEARCH

The committee is well aware of the anxious work being done on the role of viruses in cancer. This is an extraordinarily complex field in which many hopeful leads have been turned up but in which there also seem to be many unexpected blind alleys and paradoxical results. The latest advance in this research, announced only a few months ago, is the visualization by an electron microscope, and the subsequent successful extraction, of nearly pure virus from the blood of rats with virus-induced leukemia. Most of the viral research in cancer to date has been with animals yielding results that are not directly applicable to man. Scientists are now searching for possible leukemia-causing viruses in human patients. There is reason to hope that the isolation and identification of such viruses may pave the way for the development of a vaccine, but I must stress, Mr. Chairman, that in our present state of knowledge this development may still be a long way off.

INCREASED UNDERSTANDING OF VIRUSES

Perhaps the most significant long-term development is to be found in our approach to a better understanding of the nature of viruses. The long-accepted concept of viruses as entities—somewhat analogous to bacteria but very much smaller—has given way to the view that a virus may be only a phase in the life cycle of large and biologically important molecules. A chemically definable nucleic acid has been extracted from some viruses and was found to have the same infectious properties as the virus itself. It therefore appears probable that nucleic acids are sometimes contained in a corpuscular structure known as a virus and sometimes exist in a free state in which they cannot be detected even by the most powerful electron microscopes now available. Nucleic acids, which are one of the principal building blocks of living matter and play an important but not yet fully understood role in genetics, may thus also be responsible for many diseases now attributed to viruses.

GENERAL IMPLICATIONS OF NIH RESEARCH

Mr. Chairman, I said earlier that a great deal of work in biology must of necessity be empirical and pragmatic, following leads as they appear. It has occurred to some scientists in this field that they may be emerging from their confinement to independent studies relating, in one case, to heredity, in another to viruses, viral infections and the viral composition, and another to those derangements in growth that lead to cancer. All three fields are growing rapidly, and are beginning to strike across one to the other. It is conceivable that the discrete advances may be synthesized into very broad generalizations that will tie broad and important biological fields together.

Hopefully, this will be the case, but this is pure conjecture.

I have sketched these aspects of viral research to illustrate some general implications of the work:

(1) Seemingly unrelated research can result in a significant advance against disease, as it has against polio and measles;

(2) The task is enormous, as exemplified by the scores of respriatory viruses which must be isolated and identified; and

(3) The relationship between specific viruses and specific diseases is often baffling, as it is in the case of cancer.

But more important than the scope of its present problems is the fact that the whole field of virology may be on the verge of a revolution in its basic concepts. Significant future progress may well depend on the merging of virological approaches and techniques with those of biochemistry and biophysics. Although much remains to be done, and can be done, along present avenues of investigation, the answer to many disease problems will ultimately be found through basic research not only into the structure, behavior, and function of nucleic acid, but in the dynamics of the mysterious area between what we arbitrarily call nonliving and living matter.

ATHEROSCLEROSIS AND THE NEED FOR EPIDEMIOLOGICAL STUDIES

An entirely different direction which research is taking is illustrated by the problem of atherosclerosis—or so-called hardening of the arteries. The indications of current research findings that this may be essentially a nutritional disease raises questions that cannot be satisfactorily answered in the laboratory. In fact, atherosclerosis is one of several areas in which research has reached the practical limits of laboratory investigation—with the present state of our knowledge and techniques. The road to further progress now seems to lie in large-scale and long-range epidemiological studies utilizing large population groups as the basic unit of study. From a purely scientific point of view, the next logical step in pursuing the origins of this crippling disease is to observe the eating habits and conduct precise metabolic studies of large but diversified samples of our population. To obtain valid results this would mean, at the very least, the keeping of exact records of all food intake and making critical analyses of blood and excreta of several thousand people for a period of years in order to trace the relationship of their diet and metabolism to the later incidence of atherosclerosis. Such a project obviously entails practical difficulties and raises social problems with which neither the investigators nor Federal science administrators can cope. Yet an acute need for this kind of large-scale, controlled study exists. An understanding of a number of disease and degenerative conditions may well have to wait until some way can be found to meet this need or until some entirely unforseen development reveals an alternative approach to the problem.

These two areas of investigation—viral research and atherosclerosis—illustrate the extreme range of activity which biomedical research must now encompass if the attack on the dread disease is to be pressed with full vigor. The furtherance of clinical research will, of course, continue to receive full attention but it must be increasingly supported and revitalized by probing and sophisticated research into fundamental biological processes, on the one hand, and by meticulous and comprehensive observations of normal human behavior, on the other. These requirements are altering the pattern of biomedical research in this country and will create new demands on the research support programs administered by the National Institutes of Health. This committee, and the Congress as a whole, can be justly proud that it has in large measure anticipated these demands by creating the mechanisms through which the necessary support can be extended.

Status of New Extramural Programs

You will remember, Mr. Chairman, that in my opening statement and testimony at last year's hearings I discussed at some length the change that had come about in the character of the NIH grant programs and the four mechanisms which had evolved to accommodate this change. I shall therefore deal only with their present status at this point though I am, of course, ready to testify at greater length on any aspect of these programs if the committee should so desire.

GENERAL RESEARCH SUPPORT GRANTS

General research support grants—which were referred to last year as "institutional grants"—were initiated this year; the first awards were made last month for the 1962 calendar year. The purpose of the general research support grants is to provide institutions with a steady source of funds, uncommitted to any particular research or training project, to be used by them for the general strengthening and advancement of their health research and research training programs in the manner which they judge to be most effective. These grants—varying in amount from a minimum of $28,750 to a maximum of $426,672—are being made to each accredited school of medicine, dentistry, osteopathy, and public health.

The total amount set aside and used for this purpose was $20 million, which works out at just over 6 percent of the research support funds available for fiscal 1962. This sum was apportioned among the 153 recipient schools on the basis of a formula which awarded to each school an identical minimum plus an amount proportional to the level of its research activity as reflected by the value of its Federal and non-Federal grants, contracts, and gifts. In order to encourage the schools to seek non-Federal research support funds, the sum awarded in respect of non-Federal funds is proportionately twice as large as the sum awarded in respect of Federal funds.

If funds are made available, as requested in the budget now before the committee, it is hoped to extend the program for the calendar year 1963 to other professional schools and to hospitals and other nonprofit research organizations that have substantial health-research programs. For this purpose, a total of $30 million of the fiscal 1963 appropriation would need to be allotted to the general research support program. This is equivalent to a little over 7 percent of the research support funds requested and would bring the program to about half the 15-percent maximum authorized by the Congress.

Mr. Chairman, we thought that in the second year, since we have, as yet, had no opportunity to observe how these funds are utilized, it would be more prudent for us to expand the group of institutions which receives the funds, rather than to increase the funds made available to individual institutions. Next year, therefore, we will include such research institutions as the Children's Hospital in Boston, Sloan-Kettering, Massachusetts General, some of the larger hospital installations, and other profesional schools which have very substantial research programs.

We attach great importance to this new program, Mr. Chairman, because it sets a pattern for Federal support of medical research which frankly recognizes that it is in the national interest for the Federal Government to extend to the research institutions of the country a significant share of the responsibility for insuring the effective use of Federal funds in the furtherance of our general health research and research training objectives. I am confident that this approach by the Federal Government to the conduct of research bodes well for the future of the cooperative effort with research institutions which has already been of such substantial benefit to the people of this country.

RESEARCH CAREER AWARD PROGRAM

The research career award program has also been successfully launched. This program extends the patterns of support for medical scientists which begins at the predoctoral stage, to provide full career support for carefully chosen investigators selected on the basis of national competition.

The precise number to be supported at each stage will not be known until the pending applications have been considered at the March meetings of the National Advisory Councils. It is possible to report, however, that the program has been well received, that the quality of the applicants is high, and that their number will increase during the coming fiscal year.

The underlying purpose of the research career award program is to enlarge significantly the opportunity for full-time research careers which is so important to the further growth of our research effort. This program for the Federal selection and career support of individuals who are appointed to academic or career research positions in universities, medical schools, or research institutions is a unique venture on the part of the Federal Government in the furtherance of research. It, too, strengthens the alliance between the Government and the academic community in working for the common good of all our people and is, I believe, another major step forward in the evolution of a sound, long-term national research program.

CLINICAL RESEARCH CENTER PROGRAM

The clinical research center program is now in its third year, is well established and is amply proving its usefulness. Under the noncategorical portion of the program, administered by the Division of General Medical Sciences, a total of 40 grants for general clinical research centers have now been made and a number of additional applications are pending. Seventeen of these centers are now in operation. One of the first, with 23 beds, was opened in August 1960 and by January 1, this year, had admitted 354 research patients for a total of 4,811 patient-days.

Mr. FOGARTY. Where is this?

Dr. SHANNON. At Johns Hopkins. There were several that were started at about the same time. The University of Washington and Emory are two others.

Dr. HUNT. They were all among the first group. I remember that the University of Washington was the first one.

Dr. SHANNON. Some 60 research projects covering a wide range of conditions, from cancer and epilepsy to the drying of mucous membranes, have been undertaken in the Hopkins Center and the results of some have already been published. The youngest of these 17 centers admitted its first patient a week or two ago. The other 23 centers, of which 8 received their awards only a month ago, are now in the process of organizing and will come into operation during the next few months.

We believe, Mr. Chairman, that support of a general clinical research center is one of the soundest investments we can make. It is, if I may use bankers' terms, not only an investment in a growth stock but in one which will pay higher current dividends. The budget request now before you includes an increase of $6.5 million, over the amount available this year, to provide funds for about 20 more general clinical centers in fiscal 1963. During the past year several grants have been made for the creation of centers primarily concerned with childhood disorders and it is expected that a much greater number of applicants for the support of children's centers will be received during the coming year. The need for these centers, which will address themselves to interdisciplinary attacks on the congenital conditions, diseases and malfunction often found in young children, is particularly urgent.

CATEGORICAL RESEARCH GRANTS

Although I believe that clinical research is best served by general clinical centers—the ones already in operation are, in fact, concerning themselves with every one of our categorical interests—there is also a clear need for categorical centers especially in those areas of research, such as neurology and certain types of cardiovascular studies, that require a great deal of special-purpose equipment. To date, the several Institutes—and all but the Dental Institute now have center programs—have made 58 categorical center grant awards. Nearly half of these (27) were made by the Heart Institute and next highest number (11) by the Neurology Institute. The Mental Health Institute has seven, the Arthritis Institute is supporting three centers for clinical research in metabolism and rheumatic diseases and the Allergy

Institute has recently made a grant for a clinical research center which will have some bed patients but which will be heavily committed to laboratory work with outpatients in connection with intensive research in the closely related fields of allergy, immunology, and infectious diseases.

The Cancer Institute now supports nine clinical research centers but has, for various reasons, not found the centers program a particularly useful device. One of the difficulties is that the creation of a discrete bed and laboratory unit within a hospital is not the most effective way to organize clinical research with cancer patients. The chemotherapy and radiotherapy patients are usually outpatients who require no bed care while the surgical patient needs the special facilities and services of the surgical ward. The kind of complex experimental facilities for which there is a need usually requires new construction and can, therefore, not be initially supported under the center grant program. You may wish to discuss these questions further with Dr. Endicott, when he presents the program of the National Cancer Institute.

Mr. Fogarty. What have you got against the Dental Institute? I see all but the Dental Institute now have such programs.

Dr. Shannon. I do not believe we have any application to the Dental Institute or even an indication of an interest at this point in time. Have we?

Dr. Kreshover. No, sir; we have not.

PRIMATE CENTERS

Dr. Shannon. The special-purpose primate center program is making excellent progress. The first center, near Portland, Oreg., will be in full operation by May and some research is already being done there. Construction of two more centers—one at Seattle, Wash., and the other at Madison, Wisc., will begin by early fall. Three more regional centers are projected: One in Atlanta, Ga., one in the Boston area, and one in the vicinity of New Orleans. Future needs include a center for the study of the subhuman primates themselves, not as a laboratory animal for studies directed to other purposes, but as the primary subject of investigation. If research in which the primate is the essential or the most useful kind of research animal is to flourish, we need to know a good deal more about the handling, the maintenance, and the conditioning of apes and monkeys, the problems of their transport and about the suitability of various species for particular types of research.

To give an example, a marmoset is a small primate that can be handled in small cage facilities just like rodents. We have not learned how to raise and breed this small animal.

Most primate research now deals with individual animals, much as a clinician must deal with an individual patient, but much investigative work requires the study of groups of animals; and primates up to the present time, those that are available, are just not suited for that type of work.

So we feel that in addition to use of such primates as are currently available for investigative work, we need to explore and develop ways and means of raising, breeding, and nurturing the small primate, in order greatly to extend the utility of the primate in many more areas of biological research.

Also, in view of the dwindling supply of primates we must consider the desirability of substantially enlarging breeding facilities.

The captured wild primate is not suited for certain types of work.

The measles program was held up this year because all the animals arriving from India possessed measles antibody, so there was no test animal and no susceptible tissue for culture. It is very fortunate that we had a small colony in Puerto Rico and were able to find rhesus monkeys that did not have measles antibody. These served this investigation at a crucial period of time.

It is certain that there are other viruses in these so-called wild monkeys that we have no control over that must be controlled if they are to be fit for many infectious disease problems. So we have a need for a center, then, not for biological investigation of other things but for the investigation of the monkey himself, of the primate himself, his reproduction, the rearing, the handling, so as to broaden the availability of this type of animal for a whole host of investigations.

We also have a need for a production facility. Such a facility would have the additional advantage of enabling us to develop known genetic strains, a factor which can be very important in certain kinds of research. The primate centers, by providing unique facilities for a most productive type of investigation, will greatly strengthen this country's biomedical research potential. I can assure you, Mr. Chairman, that this is a most important program.

SPECIAL RESOURCES CENTERS

In addition to these four programs, the Congress last summer provided funds for a fifth—the special resources centers program. This rounds out the current array of special-purpose programs by providing support for highly specialized research services and facilities not now readily available to the institutions in which most of our research is conducted. It is, of course, too early to report in detail on so new a venture. The specific needs and opportunities in this area, and their relative order of importance, are being most actively studied with a view to developing a sound and effective program. Promising applications of electronic data processing both as a research and as a communications tool are, for example, being examined by our Advisory Committee on Computers in Research which serves not only as a review panel for grant applications in this field but which has an important role in advising me on program needs and in stimulating biomedical investigators to explore the possibility of applying EDP techniques to their research problems. I am certain that many research projects can be greatly aided and accelerated if we can make available highly skilled mathematical and statistical services and computer centers specially designed and staffed for complex biomathematical work.

I might say that of the $5 million made available for this particular program, approximately $3.2 million has been committed for the establishment of computer facilities in, I believe, some 11 locations.

The degree of precision demanded by modern medical research also requires intricate, and often specially designed, instrumentation which, in many cases, can be best and most economically provided by a central organization. Other facilities for which there is a growing need are germ-free animal colonies with appropriate ancillary laboratories for research in a germless or monocontaminated environment; marine biological laboratories, and regional reactor centers. Special resource centers making some of these research supporting facilities and services available will play a most important role in promoting medical research in this country.

These special-purpose programs have as their common objective the strengthening and expansion of the foundation on which biomedical research rests. However, their development presents quite different problems, and involves somewhat different criteria, from those encountered in administering the regular NIH research and training programs. We have, therefore, established a new Division of Research Facilities and Resources to administer these programs, insure coordination between them and serve as a focus for NIH activities in this important area. The health research facilities construction program will, if its life is extended by the Congress, also be transferred to this new Division.

This organizational change is, I think, symbolic of the new direction of the NIH programs about which I spoke last year. The general effect of giving greater emphasis to the support of the framework of facilities and resources underlying research will not only enhance our capacity for and broaden the base of medical research, but will also provide a more effective setting for the traditional project grants which remain the cornerstone of the research support system. Finally, the creation of a more adequate research environment will facilitate the recruitment of imaginative and energetic young men and women without whom the most excellent facilities will be barren and unproductive.

MANPOWER REPORT

This committee, in its report on last year's appropriation bill, asked NIH to prepare a balance sheet of estimated research manpower requirements 5 and 10 years hence, and a projection of expected output. Such a report is being submitted for your consideration. It is necessarily a large document, and it is, also necessarily, more speculative in content than its array of statistics might suggest. Projecting the future is at best an uncertain exercise. Nevertheless, I believe that it presents a reasonable estimate for both sides of the manpower ledger and that it provides a rational base for future planning.

NATIONAL EXPENDITURES FOR MEDICAL RESEARCH

The main points of this report can be briefly summarized. For want of a better yardstick, we have accepted national expenditures on medical research as a reasonably valid measure of the level of medical research. Thus our projections are made on the assumption that total national expenditure for medical research will rise to about $3 billion by 1970.

NEED FOR PROFESSIONAL MEDICAL RESEARCHERS

Expenditure per professional worker has risen sharply and steadily during the past few years and will inevitably continue to rise as a result of the increased costs of large-scale clinical research facilities;

more complex, automated instrumentation, and the accompanying need for highly skilled and highly paid technicians; and the conduct of large-scale population studies. It is thus expected that, while expenditures will increase threefold by 1970, the need for professional manpower will double. In 1954 there were about 19,000 professional workers in medical research, in 1960 there were about 40,000, by 1970 we shall need about 80,000 to mount a $3 billion research program in the Nation. Thus we shall have to more than double the current number of professional medical research investigators. In fact, we shall have to add a total of about 45,000 in the present decade to provide for the increase and to allow for deaths, retirement, and shifts to other activities. Looking at this problem another way, this country increased its crops of trained biomedical investigators by an average of 3,500 a year during the period 1954–60; however, we shall have to add an average of 4,500 a year in the period 1960–70—which is nearly a 30-percent increase in the average annual rate.

In this connection, I should point out that during the past few years we have not had to rely solely on current output of research manpower but have been able to draw on a rich pool of competent investigators. This pool was, in part, a legacy from the depression and war years when many physicians and other scientists now in medical research were otherwise employed, but it was also largely made up of Ph. D.'s in various physical sciences and in the behavioral and social sciences which, before the 1950's, did not figure very prominently in medical research. We conducted a study some time ago that showed quite clearly that new NIH grantees were increasingly drawn from the ranks of Ph. D.'s and from progressively younger age groups. This reservoir, while not yet exhausted, is now much lower, and we shall, in future, have to draw primarily on current output for new research manpower.

The production of highly qualified biomedical investigators has three distinct stages. The final stage—which, as far as NIH is concerned, is the special province of the training and senior fellowship programs of the various Institutes—is the highly specialized training of already competent physicians and, in some cases, established research scientists in techniques and problems relating to specific categorical disease interests.

The preceding stage—which is the special province of the training programs of the Division of General Medical Sciences—is the graduate training, at both the predoctoral and postdoctoral levels, of research scientists in the general and basic biomedical and other health related sciences.

The availability of candidates for training in research, is, of course, entirely dependent on the first stage of the higher education process—the output of our universities and professional schools. For this output the biomedical sciences must compete not only with other sections of science but with all segments of the economy that require professional manpower. Despite its importance, medical research cannot assert its claim to manpower to the detriment of other important national requirements; it cannot long take precedence over the provision of more physicians or the staffing of other urgent scientific efforts.

The first requirement of a sound medical research manpower policy is, therefore, the existence of an adequate total pool of M.D.'s and well-diversified Ph. D.'s. But the support of a national program to this end does not lie within the authority, the means, or the administrative competence of the NIH. This vitally important basic task is a matter of national policy which the Congress has before it for consideration at the present time.

It is not possible to make a precise analysis of the manpower needed, or likely to be available, by type of professional degree or field of study. Nor is this necessary. There is considerable flexibility in demand and considerable mobility of manpower between related fields. Provided special training programs are available as special needs arise, we need not be too concerned about attempting to make fine adjustments of supply to demand. We should aim, rather, at insuring an adequate pool of highly competent manpower to serve not only our research but our service and educational needs. Each of these needs is so great and will so clearly continue to expand that there is no danger that any foreseeable programs will produce an oversupply.

RELATION OF MANPOWER SUPPLY TO RESEARCH NEEDS

The dynamics of manpower supply and demand delineated in this report, which was completed only a few days ago, must now be related to the expected needs of the various research areas supported by the categorical Institutes. The individual training and fellowship programs can then be reviewed in the light both of the expected requirements and of the projected manpower supply. I have asked the Institute Directors to give this followup of the manpower report their urgent attention so that we may have a detailed and comprehensive plan for the further development of the training grants program in ample time for discussion with the Surgeon General and the Secretary and submission to the Bureau of the Budget for inclusion in next year's appropriation request.

The training grant and fellowship items in the appropriation request now before you are, with one exception, at the same level as in our current operating budget. The exception is in the appropriation request for the National Institute of Mental Health which includes an increase of $9,994,000 for its service-training activities because of the clearly evident and urgent needs in this area.

INTERNATIONAL ACTIVITIES

International activities have now become a significant part of the NIH programs. NIH support of medical research and research training in foreign countries, which was a very minor aspect of our program in 1956, has in the intervening years done much to stimulate interest in the biomedical sciences throughout the world. The rise in the level of research activity in other countries has presented NIH with increasing opportunities to use its grant mechanisms to enlist the participation of foreign talent and to utilize the often unique health problems that exist abroad to the common research effort. The International Health Research Act of 1960, which explicitly authorized the Public Health Service to support research and related activities in foreign countries that would contribute to the advancement of our programs, has given further impetus to the international aspects of our operations. To coordinate these activities we have established an Office of International Research, in the Office of the Director, and I shall leave it to Dr. Martin Cummings, who heads this new Office, to testify in detail concerning the international activities of NIH when he appears before the committee in connection with the foreign currency program. We have also established a small unit in Paris as an extension of the office of the science attaché housed within the American Embassy and we are now discussing the feasibility of setting up a limited number, perhaps two or three, other field offices with the science adivser of the State Department who has a keen and sympathetic interest in the furtherance of worldwide medical research and has been most helpful.

CONSULTATION WITH STATE DEPARTMENT

In developing the NIH international programs, we are, in fact, keeping in close touch with the State Department, with whom we recently worked out a new arrangement governing the international Cholera Research Laboratory at Dacca, Pakistan, and with the Federal Council for Science and Technology and the President's Science Advisory Committee who are also giving increasing attention to the Federal Government's role in international scientific affairs.

The role of the foreign program of NIH, as the International Health Research Act makes clear, is to advance the effectiveness of the health sciences in the United States.

EFFECT OF NIH GRANTS IN FOREIGN COUNTRIES

The effect of the NIH programs on the internal affairs of the countries in which grants are made is, however, of lively concern to us. We have been careful to develop these programs in a way which will benefit both the United States and the host country. This has meant, in the past, that we simply took pains to assure ourselves that a project to be supported was of mutual benefit. We have recently realized, however, that we must also make a more sophisticated assessment of the effect of our foreign grants. Although the total NIH investment in research abroad will this year amount to only a little over 3 percent of our research grant expenditure, the sum of NIH grant support may in some countries constitute a high proportion of that country's total medical research effort. We have therefore reviewed our foreign grant programs and have set up criteria which will insure that our actions do not inadvertently interfere with the healthy growth of indigenous programs either by replacing or discouraging local investment in research or by diverting their limited scientific manpower from more essential local activities such as health services and teaching.

STAFFING PROBLEMS

During last year's hearings, Mr. Chairman, I described the difficulties of retaining our senior scientific and administrative staff under the existing salary limitations. I am sorry to have to report that the loss of key members of the staff to other institutions that can offer salaries and fringe benefits we cannot begin to match is still one of our most serious management problems. And the same factor is, of course, a crippling impediment to our efforts to recruit highly qualified replacements.

While a more realistic salary scale is essential to the maintenance of the very high quality staff that NIH has heretofore been able to attract, we are also taking other measures that will help to insure the continued vigor of our intramural research and to preserve the status of NIH as a leader in medical research.

We have developed a program offering 2-year appointments as research fellows at NIH to outstanding young men and women who have just earned their doctoral degrees. These fellowships will normally be extended for a third year and at the completion of the 3 (or, in some instances, 2) years successful fellows who wish to pursue their research at NIH will be offered an opportunity for regular appointment to the commissioned corps or under civil service. This program will, we think, assure NIH of a steady supply of dynamic young research talent and provide a realistic period for evaluating potential prospective career employees.

You see, under the present system, before we make a career commitment to an individual, we do not have the opportunity to observe him long enough. And this will provide, through a program which has the full approval of the Civil Service Commission, a longer waiting period before we make the commitment of a career appointment.

I have touched on the major new program areas and on some of the special problems we face both in the substance of research and in the management of the NIH activities. There are, of course, many more items in our budget of which I have not spoken and about which the committee will wish to inquire during this hearing.

Mr. Fogarty. Excuse me.

Dr. Shannon. Yes, sir.

Mr. Fogarty. These research fellows, what do they get?

Dr. Shannon. They will get essentially the same salary as they would receive had they entered in a normal civil service appointment. But the terms of their employment are such that it will be a temporary appointment for 2 years, renewable for 1, before the career appointment is made. The salary will be the same, sir.

1963 APPROPRIATION REQUEST

Dr. Shannon. The 1963 appropriation request for the NIH operating programs totals $780.4 million. This is an increase of $103.5 million—or approximately 15 percent—over the 1962 operating budget.

As you know, the 1962 operating budget—as a result of the establishment of administrative reserves—is some $60 million less than the 1962 appropriation. But even without this unprogramed reserve, the funds available for 1962 are substantially greater than those appropriated for the preceding year. Moreover, NIH was given considerable flexibility in distributing the necessary saving among the various activities and we were therefore able to set aside the reserves in a way that permitted sound program advancement. I can assure this committee that the available funds have enabled us to maintain the momentum of all our programs.

I am equally certain that the requested 1963 appropriation, if granted, will further accelerate the pace of both our intra- and extramural research. The amount is not all that could conceivably be asked but I believe it to be adequate for the further development of a vigorous national medical research effort during the coming year. I am very happy to be able to appear before this committee to testify for a budget which I can sincerely describe as representing, in my candid professional opinion, a good forward-looking program for the NIH and a sound investment of public funds in the health and happiness of all our citizens.

AMOUNT OF ORIGINAL REQUEST TO DEPARTMENT

Mr. Fogarty. What did you ask the Department for?

Dr. Shannon. $885,314,000.

Mr. Fogarty. What did you get from the Bureau of the Budget?

Dr. Shannon. $780,000,000.

Mr. Fogarty. Between the two, they only cut you $100 million. You must have gone to them with an exceptionally good budget if they cut you back only $100 million. Did you ask for too much?

Dr. Shannon. No, sir.

Mr. Fogarty. Do you think you could use that $100 million if Congress voted it and they do not take it away from you again?

Dr. Shannon. I think we could use the bulk of it; yes, sir.

RESERVE OF 1962 APPROPRIATIONS

Mr. Fogarty. In the whole Department there are forced savings, so-called administrative reserves, totaling $55,398,000. I pointed out earlier that the Public Health Service bore over 90 percent of this; $50,773,000, to be exact.

I see that just the National Institutes of Health is bearing over 80 percent of the Department's forced savings—$44,577,000. The President said in his letter to each Cabinet officer and agency head:

> I much prefer that obligational authority remain uncommitted when there is any doubt that expenditures would yield substantial returns to the national interest.

Is there any place in the Government that you know of where expenditure of funds is more likely to yield substantial returns to the national interest?

Dr. Shannon. Well, Mr. Fogarty, I would think that we would get substantial returns. Were some of the reserves released to us, I believe we could give substantial returns.

Mr. Kelly. Mr. Chairman, may I comment on those percentage figures that you used, that what they constitute is the relationship which the increases in controllable areas in the Department represented of the whole Department. There was no attempt to make the Public Health Service stand a greater share than others. It was because the funds available, made available by the Congress in 1962 over 1961 in controllable areas were that much larger in the Public Health Service than they were elsewhere in the Department.

Mr. Fogarty. I understand that. But that doesn't make it right.

Mr. Kelly. I just wanted to explain it.

Mr. Fogarty. The percentages I have given are correct, and the figures I have given are correct, are they not?

Mr. Kelly. They are, sir. This is the reason for it.

Mr. FOGARTY. I do not agree with the Secretary or the President that these reserves should exist. The President knows it, and so does the Secretary, and so do you. It is far from being a secret.

HISTORY OF RESERVES

Did you offer up this cut?

Dr. SHANNON. No, sir.

Mr. FOGARTY. Did someone tell you you had to take it?

Dr. SHANNON. We were told that a sum of $60.4 million would be put in reserve. Of this amount, $15.832 million, had been recommended by NIH as a sum that could not be covered by programing with any precision at the time the apportionment was requested.

Mr. KELLY. That is out of the $60 million.

Mr. FOGARTY. You could give up $15 million and not be hurt; but how much did you offer in administrative reserves? Did you offer any?

Dr. SHANNON. No.

Mr. FOGARTY. So you were forced to take the administrative reserves?

Dr. SHANNON. Yes, sir.

Mr. FOGARTY. Did you make any fight at all about these administrative reserves, or did you just give in without fighting?

Dr. SHANNON. Well, I do not think it was a question of fighting or not fighting, Mr. Fogarty. This was a direct concern——

Mr. FOGARTY. Some people fight and some do not, you know, when these suggestions are made.

Dr. SHANNON. I do not believe this was a suggestion, sir.

Mr. KELLY. I do not believe these were received in the form of a suggestion.

Mr. FOGARTY. Tell me what you did. You either agreed to it or it was directed.

Dr. SHANNON. No, this was a directed reserve, it was not a proposal for discussion. It was given to us as such, and we accepted it as such.

Mr. FOGARTY. I said that there are some people that did fight. When Secretary Goldberg was before this committee, I asked him these qusetions, and asked the Secretary of Health, Education, and Welfare the same questions.

Mr. Goldberg fought this policy, directive, or whatever it was, for 3 months. And he said, in answer to a question:

> If I may say so, Mr. Chairman, we were requested by the Budget Bureau to make some economies. I want to say quite categorically that I did not feel there were any economies that we could really make. The programs that you have authorized us to make, in my opinion, are absolutely indispensable. And I have told the Bureau of the Budget and I have told the President of the United States.

He really put up a fight because he thought that these moneys should be used because he was convinced that the President's statement about yielding substantial returns to the national interest applied to his programs.

So that is an example of what I meant by some people fight and some do not.

SECRETARY'S LETTER TO AGENCY HEADS REGARDING RESERVES

Did you get anything in writing to cut these appropriations back?

Dr. SHANNON. Yes, sir.

Mr. FOGARTY. From whom?

Dr. SHANNON. The Secretary.

Mr. FOGARTY. Is that the only thing in writing you received on these cuts?

Dr. SHANNON. Yes, sir.

Mr. KELLY. Yes, sir.

Mr. FOGARTY. I think I asked the Secretary; he did not get anything in writing, did he?

Mr. KELLY. Not in terms of amount, just in terms of the statement from which you have quoted several times.

Mr. FOGARTY. I imagine that there are some people who wish they never had heard of these reserves, and they do not want any proof in the files that they had anything to do with it. That is the way it looks to me.

What was the Secretary's letter to you? Do you have a copy of it?

Dr. SHANNON. We can furnish you a copy, I am sure, sir. It was just a memorandum directed to, I think, the several agencies that were concerned. And there was a paragraph that represented——

Mr. FOGARTY. All right, put a copy of it in the record.

Dr. SHANNON. Yes, sir; I shall be glad to.

(The letter referred to follows:)

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
November 2, 1961.

Identical memorandum:
To: Operating agency heads.
From: The Under Secretary.
Subject: Reduction in obligations, fiscal year 1962.

This will confirm the Secretary's oral instructions to the heads of operating agencies with respect to savings to be accomplished against appropriations made for fiscal year 1962. Each of you was furnished a table showing the reductions by appropriation or program and, in some cases, by category.

This allocation of the reduction was developed after a careful analysis in an effort to accomplish the savings in those areas where an expansion was occurring in order to avoid any cutback in existing programs. It is intended, therefore, that the actual application of the reduction in positions and obligations will be by appropriation and by category in not less than the amounts indicated on those tables. A summary version of the table for your agency is enclosed.

If you find it impossible to accomplish the savings in the areas shown on these tables but can make equivalent savings through a different distribution, you may submit alternate plans for approval through the Office of Financial Management.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Distribution of reduction in new obligational authority, fiscal year 1962

PUBLIC HEALTH SERVICE

[In thousands of dollars]

	New obligational authority reduction			Expenditure reduction
	Extramural amount	Intramural		
		Positions	Amount	
Buildings and facilities			[1] $10,000	$500
Accident prevention	$94	11	62	150
Chronic diseases and health of the aged	631	15	562	1,000
Communicable disease activities		22	233	220
Community health practice and research	202			175
Dental services and resources		6	100	95
Nursing services and resources	21	5	61	75
Hospital construction activities	1,824	6	59	1,150
Air pollution control	89	22	336	400
Milk, food, interstate and community sanitation	163	15	99	240
Occupational health	101	1	13	90
Water supply and water pollution control	408	33	929	1,170
BSS management fund		17		
Foreign quarantine activities		8	56	53
National Institutes of Health	53,555	307	6,845	33,500
National health statistics		10	147	140
Operations, National Library of Medicine		2	170	160
Salaries and expenses, Office of the Surgeon General		4	46	44
Total, Public Health Service	57,088	484	19,718	39,162

[1] Construction items.

USE OF RESERVES IF RELEASED

Mr. FOGARTY. Now, could these—I am not talking about the $15 million that you mentioned—could these administrative reserves be used if they were released?

Dr. SHANNON. I think substantial amounts could be.

Mr. FOGARTY. I am still hoping that the Secretary and the President will change their minds on this and release these reserves or most of them before the year ends.

Dr. SHANNON. Well, substantial amounts could be utilized. We have gone over those program shortages, and were the opportunity given to us, we could present to you how we would propose to utilize them.

Mr. FOGARTY. I was going to do that for the record, anyway. I have asked everybody else.

Dr. SHANNON. This I understand. This we shall be glad to do.

(The requested information follows:)

PROPOSAL TO USE THE 1962 ADMINISTRATIVE RESERVES BY INSTITUTES

The total administrative reserves in 1962 are $60,400,000. The directed reserve to which reference is made totals $44,577,000. In addition, $15,832,000 is also in reserve. These are funds for programs which were not developed at the time the 1962 apportionment was submitted.

A current review of operating programs indicates that in the research grant, fellowships, and training activities of some Institutes the requirements exceed the funds allotted. In some instances these projected requirements are in excess of the amounts allocated in the appropriation for specific activities within the Institute.

The following table relates the amounts reserved in each activity for each appropriation with the estimated amounts which could be used if reserves were released. These estimates are contingent on the early release of funds, and are tentative to the extent that they involve predictions and assumptions concerning the results of March Council actions.

	1962 reserves			Estimated requirements in excess of allotted funds	Estimated portion of reserve which could be used—	
	Total reserve	Unprogramed funds	Directed reserve		From directed reserve	From total reserve
General research and services:						
Research grants	874	----------	874	4,555	874	874
Fellowships	293	----------	293	4,989	563	563
Training grants	1,600	----------	1,600	4,500	1,600	1,600
Direct operations	270	----------	270	----------	----------	----------
Total, general research and services	3,037	----------	3,037	14,044	3,037	3,037
Cancer:						
Research grants	11,764	4,300	7,464	----------	----------	----------
Training grants	1,275	----------	1,275	----------	----------	----------
Chemotherapy contracts	1,250	----------	1,250	----------	----------	----------
Other direct operations	1,508	93	1,415	----------	----------	----------
Total, cancer	15,797	4,393	11,404	----------	----------	----------
Mental health:						
Research grants	3,226	----------	3,226	202	202	202
Fellowships	1,548	----------	1,548	1,050	1,050	1,050
Training grants	200	----------	200	9,244	3,982	4,119
Direct operations	397	137	260	----------	----------	----------
Total, mental health	5,371	137	5,234	10,496	5,234	5,371
Heart:						
Research grants	15,392	6,000	9,392	----------	----------	----------
Fellowships	535	----------	535	1,143	1,143	1,143
Training grants	2,565	----------	2,565	928	928	928
Direct operations	1,103	225	878	----------	----------	----------
Total, heart	19,595	6,225	13,370	2,071	2,071	2,071
Dental:						
Research grants	637	321	316	----------	----------	----------
Fellowships	238	----------	238	----------	----------	----------
Training grants	1,050	----------	1,050	575	575	575
Direct operations	106	----------	106	----------	----------	----------
Total, dental	2,031	321	1,710	575	575	575
Arthritis:						
Research grants	3,716	500	3,216	4,718	3,715	4,292
Fellowships	323	----------	323	1,058	323	323
Training grants	775	----------	775	470	470	470
Direct operations	271	77	194	----------	----------	----------
Total, arthritis	5,085	577	4,508	6,246	4,508	5,085
Allergy:						
Research grants	528	500	28	2,228	232	832
Fellowships	90	----------	90	203	90	90
Training grants	50	----------	50	457	50	50
Direct operations	304	100	204	----------	----------	----------
Total, allergy	972	600	372	2,888	372	972
Neurology:						
Research grants	5,334	2,500	2,834	3,482	3,482	3,482
Fellowships	57	----------	57	----------	----------	----------
Training grants	1,235	----------	1,235	1,684	1,460	1,684
Professional and technical assistance	1,500	1,000	500	----------	----------	----------
Other direct operations	386	70	316	----------	----------	----------
Total, direct operations	8,512	3,570	4,942	5,166	4,942	5,166
Totals:						
Research grants	41,471	14,121	27,350	15,185	8,505	9,682
Fellowships	3,084	----------	3,084	8,443	3,169	3,169
Training grants	8,750	----------	8,750	17,858	9,065	9,426
Direct operations	7,095	1,702	5,393	----------	----------	----------
Total, NIH	60,400	15,823	44,577	41,486	20,739	22,277

USE OF ADDITIONAL FUNDS

Mr. Fogarty. Also, I am going to ask you how you would spend that other $100 million that your request was cut.

Dr. Shannon. Yes, sir.

Mr. Fogarty. And why these programs are necessary; and what programs are going to be held back because of this cut of $105 million. Give us these things for the record.

That figure is a combination of the Bureau of the Budget and the Department cuts, isn't it?

Dr. Shannon. Yes, sir.

Mr. Kelly. Yes; it is.

Dr. Shannon. The Department supported $855 million to the Bureau of the Budget.

Mr. Fogarty. They only cut it $30 million?

Dr. Shannon. Yes, sir.

Mr. Fogarty. Well, give us a breakdown of that $30 million and then the other cut by the Bureau of the Budget. We will have two tables.

(The requested information follows:)

Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health—Activity distribution of the reduction by the Department of Health, Education, and Welfare and Bureau of the Budget [1]

	By the Department of Health, Education, and Welfare	By the Bureau of the Budget
Grants and related contracts:		
Research:		
Regular program	−$11, 775, 000 +2, 000, 000	−$28, 528, 000 +3, 400, 000
General research support grants	0	0
Scientific evaluation grants	0	0
International centers for medical research and training	0	0
Gorgas Memorial Laboratory	0	0
Clinical research centers:		
General	−6, 500, 000	0
Categorical	0	−12, 500, 000
Special resource centers	−2, 500, 000	−2, 500, 000
Primate centers	−3, 000, 000	−5, 000, 000
Total research	−21, 775, 000	−45, 128, 000
Fellowships		−5, 084, 000
Training		−16, 250, 000
State control programs	−-3, 250, 000	
Community demonstration projects		
Total, grants and related contracts	−25, 025, 000	−66, 462, 000
Direct operations:		
Research	−1, 500, 000	−2, 140, 000
Collaborative studies	−3, 000, 000	−3, 060, 000
Biologics standards	0	+631, 000
Training activities	−100, 000	−89, 000
Professional and technical assistance	0	−1, 303, 000
Review and approval	−548, 000	−1, 964, 000
Administration	−141, 000	−213, 000
Total, direct operations	−5, 289, 000	−8, 138, 000
Total	−30, 314, 000	−74, 600, 000

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[1] Some of the activity dilstributions were negotiated with the National Institutes of Health.

EFFECT OF 1962 RESERVES ON 1963 BUDGET

Mr. KELLY. The large proportion of the Bureau of the Budget reduction related to the application of the reserves in 1962. They continued application of those reductions in 1963.

Mr. FOGARTY. I am still confused about the way you allocated these cuts.

Mr. KELLY. Well, in connection with the National Institutes of Health, we arrived at the total amount of the reduction and the amount of it which had to be intramural and the amount which had to be in extramural, but we collaborated with Dr. Shannon and the Surgeon General in determining by Institute and by activity how this could best be taken in order to carry out the most urgent parts of their program.

AUTHORITY FOR RELEASING RESERVES

Mr. FOGARTY. Since these reserves do not exist so far as the formal apportionments are concerned, why cannot the Secretary on his own initiative release them?

Mr. KELLY. I think because it would not be in good faith because of his submission to the Bureau of the Budget and the President and the agreement as to the amount of the reserve. I think it could only be released by the President.

Mr. FOGARTY. I think the Secretary can do it. I do not know what the reaction would be, but I still think he can release these reserves. But suppose the Secretary did tell the President that he had come to a decision that this was a mistake and that he was going to release these reserves. Do you think the President would object?

Mr. KELLY. Well, I think that if he told him, the President would be likely to object. I think he might ask and get his consent.

Mr. FOGARTY. Do you think that if he was asked, he would consent?

Mr. KELLY. I have no idea, sir.

Mr. FOGARTY. Well, I am going to ask him when we get this record complete; the Secretary, too.

NIH STUDY OF SALARY STRUCTURE

We had some comments in our report last year that affected more than an individual Institute. One of them was on the problem of your salary structure. You are having a study made now on that?

Dr. SHANNON. Yes, sir. That, I think, Dr. Terry described briefly to you. This is a salary study; rather, a study of the personnel system, including salaries, conducted by a panel headed by former Secretary Folsom, that we expect will report by the end of this month. Meanwhile, there has been no opportunity to press forward with independent action.

Mr. FOGARTY. I understand.

Mr. KELLY. I think, in addition to that study, Mr. Chairman, you have the President's indication that he is going to send a pay reform bill to the Congress, so that the salary structure that last year we were concerned about only with respect to the 208(g)'s is now being considered in terms of the total civilian personnel force.

RESEARCH COMMUNICATIONS

Mr. FOGARTY. We also mentioned the weakness in communication of the results of research. What have you done about this?

Dr. SHANNON. Well, in the first place, you asked for a report, Mr. Chairman. I have a preliminary report but I would prefer, if I may, not to submit it now, because I do not think it fully portrays either the problem or the steps that we can take to tackle the problem.

Quite frankly, sir, this is an illustration of the shortage we have in the top personnel at the National Institutes of Health. We did not get to the report early enough to complete it. With the other programs we had to mount, this had lesser priority, for example, than the manpower study. At this point I do not have a report that I should like to submit to you.

Now, I do think that I can commit the National Institutes of Health, if you propose to have hearings with outside witnesses, to intensify our efforts with this and have this report to you before those witnesses——

Mr. FOGARTY. They are going to be here again.

Dr. SHANNON. When will they be here, sir?

Mr. FOGARTY. Around the first week in March or second week.

Dr. SHANNON. This would give us sufficient time, I think, to rework the present report into an adequate document. If we could have your permission to delay this, I would be most appreciative.

Mr. FOGARTY. Fine.

(The document referred to appears on p. 1594, et. seq.)

INSTRUMENTATION PROGRAMS

What about instrumentation?

Dr. SHANNON. The work that has been done on instrumentation is twofold. Firstly, we have had several study groups who have been developing programs that we might undertake within the framework of our operation.

Secondly, we have earmarked approximately $2 million of the $5 million of the special resource programs to get a certain number of those programs underway. These activities have been carried on in parallel with those that relate to the computer centers. Before the end of the year, we probably will have made as many as three substantial grants in the area of instrument development.

We know, as a result of the discussions of study groups and seminars during the past year, that in the year to follow we shall have very broad requests for support activity in this particular area.

The program relating to instrumentation is well underway, but is a step behind the computer program.

NEED FOR GOOD LIBRARIES

I want to emphasize this about the problems of communication. First, from the standpoint of the down-to-earth, the day-to-day transmission of information, from educator to student, educator to practitioner, or professor to his young developing scientist, or from the scientist to the practically oriented man: Such communication depends, in the first instance, on good libraries. And then you look at the library structure——

Mr. FOGARTY. We do not have good libraries.

Dr. SHANNON. No, sir; we do not have good libraries. And half of the medical school libraries in this country, I am given to understand, are not administered by good professional librarians.

Mr. FOGARTY. We have a great lack of good libraries.

Dr. SHANNON. This is particularly apparent at the smaller medical schools. They do not have adequate reference material to conduct a sound educational program. So the big job, the one thing I really think we should do first and do now, is to strengthen our library system. Rather than worry about the rather fancy Buck Rogers projects, we must satisfy the day-to-day medical needs and provide research and educational institutions with adequate libraries, adequately stocked, adequately administered. This is the real crying need.

The second problem is well within the techniques currently available and in the responsibility of the National Library of Medicine. This relates to the secondary handling of information; that is, the development of adequate bibliographies, the development of adequate review journals or summaries, things of this sort. The National Library of Medicine is now getting into this field in a vigorous fashion.

Then for the longer haul, is the problem of adapting electronic equipment to the storage and handling of information. Not for today, but for a decade from now.

Too frequently when the problem of communication is brought up in discussion, one hears only of the ultimate in electronic techniques and forgets the more important day-to-day work in the library. Now, I think that the second look——

Mr. FOGARTY. You have been talking about this problem for 15 years, to my knowledge. I remember Mr. Keefe bringing it up when he was chairman of this committee.

PROBLEMS OF MEDICAL COMMUNICATION

Dr. SHANNON. There is a second way of looking at it. We have been talking about the transmission of new knowledge for education, for the development of scientists. There is the other type of science education that relates to the scientists as a practitioner. Now, this involves a whole array of quite different techniques, in different forms, different professional societies, and different professional channels.

And finally, but equally important, is the very complex job of transmitting sound medical information for popular consumption so that individuals may have a better appreciation of what health is and what disease is.

So when one talks about communication within the medical sciences, one is discussing an extraordinarily broad and very complex area for which there is no single simple answer. The report that we are preparing will be concerned primarily, if not exclusively, with those areas of science that relate to research and with the transmission of research findings to the young developing scientist and to the young student being educated. I think, as Dr. Terry has pointed out, that the Library of Medicine has a role to play in this, the Bureau of Community Services has another large role to play, and if we can restrict our report to you to the area that is primarily ours, I think——

Mr. FOGARTY. Well, that will be some progress. I would like to see something started this year.

Dr. SHANNON. Yes, sir.

Mr. FOGARTY. If you need some more funds to get some of these recommendations going, we will ask you what you need.

Dr. SHANNON. I suspect that what we need is a working conference sort of thing that will bring 5 or 6 or 10 people together over a period of 5 or 6 months during which they can intersperse small group meetings with substantially larger ones. This is like the weather; everybody talks about it but nobody does anything about it.

Mr. FOGARTY. I think it is important. Is it not?

Dr. SHANNON. I believe it is, sir; yes.

Mr. FOGARTY. Now, training. I guess we had better not go any further. Training is a big subject.

We shall recess until tomorrow morning at 10 o'clock.

THURSDAY, FEBRUARY 8, 1962.

Mr. FOGARTY. The committee will come to order.

DRUG DISCOVERY TO TREAT HERPES SIMPLEX

Doctor, last night when we had finished we were about to start discussing training. But before we do, 3 or 4 days ago I read an article in the Wall Street Journal. A new drug had been used by someone in Boston in treating some kind of eye disease.

The point that was being made in the article was that this was a drug that was developed for the fight on cancer and apparently it didn't work there, but it did work for this particular eye disease.

Dr. TERRY. This is a drug that was developed apparently in the chemotherapy program and was used in the treatment of herpes simplex in the eye.

Mr. FOGARTY. I thought it was a good example of the way some of these funds are expended It is not necessarily true that, if you spend money on research in cancer, it is only going to affect cancer. This one, apparently, has been very successful in the treatment of this blinding eye disease.

Dr. SHANNON. This was an important advance. Dr. Mider has recently looked into its background and may like to discuss it.

NATURE OF HERPES SIMPLEX

Dr. MIDER. Mr. Chairman, the virus of herpes simplex is the virus that causes cold sores. It can also affect the eye and, under certain circumstances, the disease in the eye may lead to blindness.

Dr. Kaufmann, who was formerly with the National Institute of Neurological Diseases and Blindness, and is now at the Massachusetts Eye & Ear Infirmary in Boston and who will soon become professor of ophthalmology at the University of Florida, has used iododeoxyuridine applied locally to the rabbit eye infected with herpes simplex and has found it very effective in stopping the disease.

He has had substantial experience in treating the same condition in patients. When he reported this at a meeting of virologists in New

York City last week, everyone was impressed with the evidence that the drug did have a specific effect against the virus of herpes simplex.

Mr. FOGARTY. What is this eye disease called? How does it affect the eye?

Dr. MIDER. It is called a keratitis. It increases the thickness of the coating over the cornea of the eye. If it is not treated promptly, or if there are complicating factors, an opaque membrane develops over the eye and causes blindness.

HISTORY OF DRUGS DEVELOPMENT

Iododeoxyuridine is a direct outgrowth of which 5-flurouracil was first synthesized by Dr. Charles Heidelberger at the University of Wisconsin. It is a drug which has been of interest in cancer chemotherapy and has some effect on some intestinal carcinomas.

Dr. Heidelberger was also the first one to synthesis flurodeoxyuricline, but someone else—I believe Dr. Arnold Welch, of Yale—made iododeoxyuridine, in which Dr. Kaufmann is interested.

Bromodeoxyuridine, which is related to iododeoxyuridine, has a similar effect on herpetic keratitis. This is one of the very first drugs to have had a specific effect against a virus.

EFFECT OF DIRECTED RESEARCH ON RELATED PROBLEMS

Mr. FOGARTY. Similar things have been happening in other fields, haven't they? We have been told from time to time what we are doing in heart research may affect other diseases, not necessarily just heart problems.

Dr. SHANNON. I think that can be brought out by two general examples. In the cardiovascular field, the study of the mechanisms whereby certain hormones produce an increase in blood pressure, led to the isolation of a substance called seratonin, which is related to epinephrine. It turns out, from further investigations of seratonin and its biological activity, that it is one of the hormones of outstanding importance for the control of central nervous system activity and is involved in the actions of many of the drugs which are presently being used to set moods in both the normal and mentally ill.

You will remember that the active materials derived from Rauwolfia, an Indian drug which was brought to this country first because of its blood pressure lowering ability, set the stage for the development of tranquilizers within a 2- or 3-year period.

I think that the lesson to be drawn is that most screens for a particular biological activity turn up chemical compounds that are active in more than a single biological system. Although attention may be called to them in relation to the specific biological activity for which the screen was set up, they may prove to have other, more important, effects. The first use is quite frequently not the ultimate use of the compound.

A good deal of the work going on in medical research today relates to the further study of active compounds found unsuited for one situation in order to determine the extent to which they can be adapted for other situations.

POTENTIAL OF IODODEOXYURIDINE

Mr. FOGARTY. Did you want to say something else, Dr. Mider?

Dr. MIDER. Just one other point, Mr Chairman This same drug, iododeoxyuridine, has been shown by Dr. Kaplan and his associates at Stanford University, and by scientists at the National Cancer Institute, to increase the sensitivity of cells to X-rays.

While the work at the present time is primarily concerned with tissue cultures, this is one possibility, at least, of enhancing the effects of therapeutic irradiation.

So they are useful in cancer as a direct chemotherapeutic agent; useful in the virus disease; and they may be quite useful in improving the sensitivity of tumor cells to X-ray therapy.

STUDY OF TRAINING NEEDS

Mr. FOGARTY. That is good. I was going to ask you about training. The committee requested that the NIH prepare, before this year's hearings, a balance sheet of estimated research manpower requirements for 5 and 10 years hence, and a projection of output. You have a report on this.

This has been giving us some trouble. We receive more complaints from deans of medical schools about this, than any other phase of your operations.

Do you want to start off by saying again your reasons for holding this fairly steady for a year and taking a good look at it? You go ahead in whatever way you think best.

Dr. SHANNON. First, in developing last year's budget we were impressed by the very rapid increase in funds available for training and the tendency to use these funds to expand still further training areas and training mechanisms already established.

We felt that, with the rapid increase we had experienced over a period of 3 or 4 years, it would be wise to see where we were moving with the programs available to us and determine whether it might not be wise to rechannel certain of our further efforts.

The second factor that led us to believe that a delay of a few months for review might be worthwhile was that we were launching the general research support grants program making wholly new funds available to universities. We felt that this new money could be used for training programs by those schools that felt particularly critical needs during the period of review and that the training programs could continue to develop without special needs for further funds from a centralized source during this year of inquiry.

Further; in studying the programs, we became aware of the fact that we were taking an increasing number of non-U.S. nationals into the training program which seemed to indicate that in certain areas we were providing more training opportunities than our own nationals could take advantage of.

We also became increasingly aware that the borderline between training of scientists for research and straightforward residency training for medical specialists was becoming blurred. This is not to say that support of training for residencies or for medical specialists is not important; but we felt that broad training of that type is a problem that is really outside the province of the NIH programs, at least in terms of what we have defended in our budget presentation in the past.

It was for those reasons that we felt, (1) that we should pause for a period of a year of inquiry; and (2) that we could do so without seriously hampering the ongoing training program.

In arriving at that conclusion, we were also well aware that, quite apart from the NIH programs, the Federal Government is very extensively involved in the training of scientists in this country, without however having evolved a broad general policy under which such training should be supported.

ORIGIN OF TRAINING FUNDS

Training funds came, directly or indirectly, from the Department of Defense, the Space Agency, NSF, the Office of Education, and ourselves, with each of us setting up segments of training to satisfy our own specific needs in terms of our understanding of our own mission. It has been estimated that, in the aggregate, some 90 percent of all graduate students in the sciences are at the present time in part supported directly or indirectly by the Federal Government. Nevertheless, no broad philosophy for this activity has evolved.

It is not our purpose to use the National Institutes of Health training program to attempt to solve all of the training problems of the Federal Government. But we did feel that we were dealing with a sufficiently homogeneous group of related subjects that it would be possible for us to introduce certain general unifying concepts—certain broad general policies—that would satisfy our needs and provide a backdrop against which the individual training programs could evolve.

I think that the study during the past year of the programs in the Institutes and the manpower survey that the House requested now provide a sound basis on which we can discuss with the Institutes how their legitimate objectives can be achieved in terms of specific manpower requirements and how, on the other hand, the biological and medical sciences, that are our responsibility, can develop in a more logical fashion.

We have now reached a point at which the NIH must address itself to the support of graduate education in the sciences relevant to our mission as a field in itself, as well as to the training of individual scientists to satisfy specific research needs.

Mr. FOGARTY. When you refer to "scientists," what is your definition of a scientist?

Dr. SHANNON. When I say scientist, I use the word interchangeably with a research worker.

Mr. FOGARTY. M.D., Ph. D.'s?

Dr. SHANNON. Both M.D.'s and Ph. D.'s and those with other degrees such as doctors of veterinary science—professionals in all those sciences that it is important should address themselves to the problems with which the NIH is concerned.

Mr. FOGARTY. When was the report finished?

Dr. SHANNON. Just a few days ago, sir.

Mr. FOGARTY. You haven't had a chance to make any recommendations with regard to the 1963 budget?

Dr. SHANNON. No, sir.

MANPOWER REPORT SUMMARY

Mr. FOGARTY. Have you made a summary of the report?

Dr. SHANNON. Yes, sir. I would suggest that the summary, which is quite short, might perhaps be included in the record, Mr. Fogarty, and I could highlight a few points.

Mr. FOGARTY. This report will undoubtedly be an important source of information for many people, and perhaps for years to come. I think we will print it as a separate hearing volume. But now would you give us a summary of the report?

Dr. SHANNON. Basically the summary says that, if we accept as a reasonable estimate a total medical research program of approximately $3 billion a year in 1970, then we shall have to develop adequate scientific personnel so that these funds can be spent effectively but without at the same time doing a disservice to related areas of activity.

In other words, we are now taking into the research process a sufficient number of M.D.'s that we feel it would not be to the best total interests of the country to increase the number of M.D.'s being brought into the medical sciences without at the same time broadening the total pool from which they are drawn.

In a somewhat similar way, our programs have not materially contributed to the pool of Ph. D.'s that is developing in this country. Yet we are taking an increasing number of Ph. D.'s into the research programs supported by the National Institutes of Health.

Without programs to expand the pools from which these people are selected, we shall leave uncovered or make difficult some of the new programs that relate to space and nuclear energy and the like.

SCIENTIFIC PERSONNEL DEVELOPMENT PROGRAMS

We feel that it is our obligation, if we look forward to the utilization of a much greater number of scientific personnel, to address ourselves, at the very least, to the support of those activities of government which tend to expand the pools from which our people will be drawn.

The importance of the problem stems from the fact that we are talking about a very large number of people. We are talking about an increase in the professional manpower needed to address itself to our problems of as many as 40,000 people between now and 1970.

SCIENTIFIC SUPPORT EQUIPMENT AND PERSONNEL

The second general conclusion to be reached from this manpower study is that if we are to mount a program of the size necessary, we must considerably expand both the physical resources available to the scientists and to the technical support the scientist needs as the subject material gets increasingly complex.

This means more facilities, more machines, and more technicians in support because without these the scientists cannot be productive.

There is a third conclusion. Before we can mount this type of program—first to train and then to utilize the scientists that are trained—our programs must evolve to provide key support to institutions as institutions.

We must go further down the road in partnership with institutions so that the needs and requirements of the institutions themselves are satisfied quite apart from satisfying needs of the individual scientists that comprise these institutions.

The elemenst of the program by which this can be accomplished are already at hand. We have general research and training grant authority—though it may well be that the present maximum of 15 percent of total research grant funds for the general institutional research support will be inadequate to achieve those ends. We also have a program which established greater opportunities for research careers in these institutions.

I think the final conclusion is that we must foster graduate education of a type that takes advantage of the total faculty group rather than graduate education limited to the support of individuals in separate departments or even subunits within departments.

EXISTING LEGAL AUTHORITY

I believe that we have the legal authority to do all these things, but I would point out, that without favorable action on some of the bills now before the Congress relating to medical school construction, to Federal aid to education, and to scholarships, the total research effort will be very gravely hampered by the inadequacy, both qualitatively and quantitatively, of the pool of professionals from which we must select research workers.

Mr. FOGARTY. The report then clearly indicates that there is a shortage of trained scientific personnel and something ought to be done about it.

Dr. SHANNON. Yes, sir; that certainly is in prospect.

IMPLEMENTATION OF REPORT RECOMMENDATIONS

Mr. FOGARTY. You have been working on this a year now and you have the report. Notwithstanding any appropriation limitations, what do you think has to be done now if we are to implement this report in 1963? Try to reduce it down into dollars for us, element by element?

Dr. SHANNON. Mr. Fogarty, at this time I think I can give you the elements as we see them. It will be another couple of weeks before we can reduce it to dollars because we are now just beginning our discussions with the Institutes on their needs.

Mr. FOGARTY. All right; go ahead and talk about the elements. Then we will ask you to deliver to the committee the estimates of what you think it would cost in addition to what we have in the budget now for 1963 to meet the need as shown by the report.

FELLOWSHIP PROGRAMS

Dr. SHANNON. Mr. Fogarty, we are impressed first by the extraordinary success we have had with the fellowship device.

Mr. FOGARTY. What about the career research professorships? Isn't that one of them?

Dr. SHANNON. Yes, sir; that is one of them. I would like to come to that later.

What I have in mind is the use of the postdoctoral fellowship as an introduction—an advanced introduction—to science. The percentage of former fellows who now have full-time academic positions, who are fully engaged in academic work and in research, is between 60 and 70 percent, which is extraordinarily high. A still larger percentage is involved, if you include all those who spend better than 50 percent of their time in research.

We feel that this program should be considerably expanded. On the other hand, relative to the intake of M.D.'s and Ph. D.'s, and in view of the broadening base of the medical sciences, we feel that we must reach down below the postdoctoral fellowship level and considerably expand the number of students we support at the predoctoral level, particularly in those sciences that are now turning out to be so important to the progress of medical science.

At the same time, there is also an increasing number of brilliant students who would like to enter medical research with an M.D. degree, but not by the conventional 4 years in medical school. Several of the medical schools have approached us about developing a specialized educational program of perhaps 5 or 6 years that would provide training and experience roughly equivalent to a combined M.D. and Ph. D. degree—although they might get only one degree.

So we would say that, in order to expand the base—the pool from which to select our career research scientists—one would need to expand predoctoral fellowships and expand the opportunities in medical schools—not simply to produce M.D.'s but to develop medical scientists in a broadly conceived scientific environment through specialized programs at the predoctoral level.

Then, as I said, we would need to expand postdoctoral level support. The career development awards have been increasingly sought after and are becoming increasingly effective as they become articulated with the career awards, which pick up the individual at about the time he attains professional rank.

CLINICAL RESEARCH TRAINING

On the other hand, while we feel that we have a very good start on the career awards themselves and that this program will grow progressively with time, there is no real urgency for expanding this particular program at this time.

All the foregoing is focused on the broad areas which emphasize fundamental rather than applied research. However, as the Division of General Medical Sciences has expanded and developed training programs of this general sort, it is also becoming increasingly important for the categorical institutes to highlight their needs for the specialized type of personnel to further their specialized missions. With the development of broad clinical research opportunities through our clinical center programs, we must address ourselves to training clinical scientists in depth.

Given the opportunity to expand training in the clinical sciences in proportion to the needs and opportunities for trained investigators, our attention will be directed to developing environments that can provide a unique type of training for an investigative career, rather than attempting to subvert normal residency training, which is designed to turn out a medical specialist, into training both for the specialist and for the scientist.

This will require negotiation with some of the board-certifying agencies. We feel that the area of clinical investigation, which will be so important in the coming decade, must be provided with individuals who are trained much more broadly and in considerably greater depth than many who are entering research at the present time.

Too frequently today, the embryo developing scientist goes through a period of clinical experience and then, after 3 or 4 years in a hospital, can only become an independent scientist by holding a postdoctorate fellowship for 2 or 3 years.

We feel that certain clinical environments should be modified to provide scientific training in association with the clinical training. This is now done in many places, but the practice should be more widespread and much broader scientific training should be provided. In this way the deficiencies in a man's background could be made up during this period of time and we should have the basis for the production of the broadly trained clinical investigators who are so badly needed.

This, then, would be a major responsibility, as we see it, of the categorical Institutes.

MENTAL HEALTH

We also find that certain areas are grossly neglected. We find, for example, as we push further, particularly in mental health or in mental health and associated somatic diseases, that the behavioral sciences have been more or less left out of our program, except insofar as they received limited support for their direct relevance to the mentally ill.

DEVELOPMENTAL SCIENCES

In dealing with the problems of the developing child, we have very little basis for setting up norms of development, whether this be emotional or intellectual development. For example the key to early development of the child may perhaps be found in studies of language development and the like. In general the various behavioral sciences have not found adequate representation in our programs.

Support for the developmental sciences related to the embryological development of the child, growth patterns, et cetera is grossly deficient.

IMPORTANCE OF ELECTRONIC COMPUTERS

As computers become increasingly important to our programs—or rather if we are to take advantage of these capabilities—we must address ourselves to the training of applied mathematicians. At the present time we do almost nothing in those areas.

So I would say that we must develop broad new mechanisms. Initially we should like to emphasize the fellowship route, whether it be predoctoral, postdoctoral, the development type or the career type.

We should like to emphasize the medical school as a place for the development of scientists by design rather than by accident. We should like to emphasize the clinical sciences as an area of training of greater breadth and depth. And we should make up some of the substantive deficiencies that result from newly acquired responsibilities in research.

This is a very complex problem, Mr. Chairman. We will do our best.

Mr. FOGARTY. We shall place your estimates of the dollar amounts for each element in the record.

(The requested information follows:)

REVIEW OF NIH TRAINING NEEDS THROUGH FISCAL YEAR 1963

PART A. DEVELOPMENT IN CALENDAR YEAR 1961 OF NIH PROPOSALS FOR THE TRAINING AND FELLOWSHIP BUDGETS FOR FISCAL YEAR 1962

In the course of the congressional appropriation hearings during the spring of 1961, both the House and the Senate committees directed the National Institutes of Health to prepare estimates of the demand for and supply of scientific manpower in 1965 and 1970. As a part of this study, the Institutes comprising the NIH were asked to prepare estimates for the various fields for which they are responsible. These studies were not completed until early in 1962. Meanwhile, the process of preparing proposals for the fiscal year 1963 had to go forward.

Before the studies were completed, it became evident that substantial increases in training and fellowship funds would be needed in fiscal year 1963. Reflecting these needs, the various Institutes prepared in May 1961 the following preliminary statements of requirements.

Institute	*Amount (in thousands)*
Total	$211, 823
Fellowships	45, 533
Training	166, 290
DGMS	60, 785
Fellowships	15, 785
Training	45, 000
NCI	16, 970
Fellowships	5, 150
Training	11, 820
NIMH	54, 540
Fellowships	6, 290
Training	48, 250
NHI	22, 100
Fellowships	5, 100
Training	17, 000
NIDR	$9, 797
Fellowships	2, 277
Training	7, 520
NIAMD	19, 550
Fellowships	3, 500
Training	16, 050
NIAID	13, 731
Fellowships	3, 981
Training	9, 750
NINDB	14, 350
Fellowships	3, 450
Training	10, 900

These proposals of the Institutes were reviewed, and the following conclusions were reached in September 1961:

(1) Extension of Institute training programs into new areas was agreed upon as warranted.

(2) Substantial increases proposed by the Institutes for existing programs were not considered reasonable because the general basis for substantial increases in existing programs was under study. Until the manpower studies indicated the long-range supply and demand picture, it was felt that increases should be held to a minimum.

These concerns were reflected in a fiscal year 1963 budget proposal for training and fellowships, 21 percent below the level proposed by the Institutes, summarized as follows:

Activity	Amounts (in thousands)		Decrease	
	Institute proposals	NIH proposals	Amount	Percent
Total	$211, 823	$167, 080	$44, 743	21
Fellowships	45, 533	31, 080	14, 453	32
Training	166, 290	136, 000	30, 290	18

By Institute, the NIH proposal was as follows:

Institute	*Amount (in thousands)*
Total	$167, 080
Fellowships	31, 080
Training	136, 000
DGMS	43, 480
Fellowships	11, 480
Training	32, 000
NCI	12, 900
Fellowships	3, 400
Training	9, 500
NIMH	51, 596
Fellowships	4, 740
Training	46, 856
NHI	18, 894
Fellowships	4, 450
Training	14, 444
NIDR	$6, 430
Fellowships	1, 230
Training	5, 200
NIAMD	13, 000
Fellowships	1, 800
Training	11, 200
NIAID	7, 800
Fellowships	1, 900
Training	5, 900
NINDB	12, 980
Fellowships	2, 080
Training	10, 900

This proposal, with accompanying justifications, was sent forward to the Office of the Surgeon General as the position of NIH and was ultimately presented to the Bureau of the Budget as part of the proposal of the Department of Health, Education, and Welfare.

The President's budget held training and fellowships to current levels except with respect to the training of personnel for service to the mentally ill. A $10 million increase for training of service personnel in mental health was allowed. In summary, the departmental proposal compared as follows with the President's budget:

Activity	NIH proposal	President's budget	Decrease	
			Amount	Percent
Total	$167, 080	$145, 746	$21, 334	13
Fellowships	31, 080	25, 996	5, 084	16
Training	136, 000	119, 750	16, 250	12

PART B. IMPLICATIONS OF MANPOWER STUDIES FOR FISCAL YEAR 1963 TRAINING AND FELLOWSHIP ACTIVITIES

The studies relating to medical research manpower were completed after the NIH proposal for fiscal year 1963 training and fellowship activities was prepared. These studies have produced an array of findings pertinent both to broad national programs for expansion of the pools of relevant scientific talent, and more narrowly to NIH programs. This statement constitutes a professional judgment of needs related solely to the NIH programs, taking into account the findings and conclusions of the study.

The primary findings of these studies as they relate to the rate of growth and the objectives of NIH training programs is that there will be continuing shortages of manpower trained for research through 1970. This will call for a steady expansion of training programs to assist in doubling the supply of manpower for medical research by 1970. The expansion must be designed to meet not only a general increase in demand for scientifically trained people, but to deal with specific definable problems.

Among the specific problems are:

1. The need to exert positive recruitment efforts to attract an adequate proportion of highly talented people for medical research in the face of sharp competition from other fields.
2. The need to expand not only numbers of scientists, but scientists with specific kinds of training foreseeably in particularly short supply over the next 5 to 10 years.
3. The need to strengthen the institutions responsible for the education of scientists.

Apart from the general perspective on needs provided by the manpower studies, the continuing and expanding involvement of the United States in international medical research will generate manpower training requirements.

Under the budgetary level of $167 million proposed by NIH for fiscal year 1963, much of the continuing evolution in purpose, direction, and scope indicated by the studies as needed to meet definable needs could be financed. There would be, however, some deficiencies in both scope and content of programs.

The specifics of an NIH training program for fiscal year 1963 to meet both currently pressing and longer range requirements are as follows:

1. The existing predoctoral fellowship program should be substantially expanded as a recruitment device for the sciences related to medicine.

2. The existing medical student research program, designed to expose selected undergraduate medical students to research, should be expanded. In its modified form it would provide an opportunity for a proportion of the most able and scientifically inclined students to derive a rigid scientific education within the general perimeters of an enriched medical experience. The primary purpose would be to develop promising scientists who, in addition, acquire an M.D. degree.

3. The existing program for recruiting selected undergraduate medical students for academic life requires a complementary program designed to provide opportunities for scientific-clinical training above the undergraduate medical level.

Existing programs do not provide for deliberate efforts to train clinical scientists through specifically planned programs designed to turn out both larger numbers of persons with these skills, and to do so by fitting the content of the training—clinical and nonclinical—to the production of rigorously trained scientist-clinicians. The absence of such a positive approach to the scientific training of clinicians has generated pressures for the support of residency training as a relatively ineffective way to produce scientist-clinicians.

A well-designed effort to meet this need would encompass provision of opportunities both in areas not specifically related to disease, and in areas linked to study of diseases. The former would be provided primarily through the Division of General Medical Sciences and the latter through the Institutes. To initiate this program, about 400 persons with M.D. degrees would be selected for specifically designed work involving planned integration of advanced scientific training with clinical investigation. With initiation of such a program, residency-type training would be encompassed as part of the combined clinical research training program. Residencies as such would not be supported. The budget for such a program would approximate $6 million, with $3 million administered by the Division of General Medical Sciences, and the remainder by the various Institutes.

4. The long-range outlook for scientific manpower in medical research has as one basic characteristic the need for a large, strong group of medical and biological scientists whose interests and training are such that they are not limited to study of the specialized aspect of a disease problem. Unpredictable changes in the areas of study which will prove most promising in the future is the basic reason for stressing training of this sort. In addition, specific areas of science are of particular significance to medical research currently in the predictable future. These areas are the behavioral sciences, the physical sciences and engineering as applied to biology, health and disease. All Institutes share responsibility for such training, but the Division of General Medical Sciences not only bears particular responsibility for these, but the NIH proposal for this Institute increased by only 8 percent above the 1962 operating level, in contrast with a 23 percent overall proposed increase in training activities. An increase of $3 million is proposed in the training budget of DGMS to meet these requirements.

5. The existing postdoctoral fellowships and graduate training programs designed to provide advanced training for research, including clinical investigation, should be extended. The use of these programs with the primary intent of training people for provision of medical service will be confined to the National Institute of Mental Health.

6. Review of manpower requirements has shown that future dependence upon the Ph. D. in medical research will be even greater in the future than has been true in the past. This dependence will extend to parts of the university outside the medical school, and particularly to graduate departments of arts and sciences. This dependence has been met in the past by provision of aid to the training of individual candidates for the Ph. D., and for their postdoctoral training. With more extensive commitment of faculty time and of resources to the production of Ph. D.'s for medical research, graduate departments themselves will need support. The eventual patterns of such support cannot be foreseen in detail at this time. For example, the general research support grant may eventually meet a substantial part of these needs. But this is not certain. To develop pilot patterns of support for parts of graduate schools (such as divisions of biology or departments concerned with sciences relating to life processes) departments producing significant numbers of scientists for medical research, $1 million would provide funds adequate in an initial year. These funds would be administered by the Division of General Medical Sciences.

7. Apart from needs indicated by the manpower studies, training requirements for the international medical research responsibilities of the United States are becoming progressively more acute. These requirements are of two kinds—training of foreign nationals in the United States and training of U.S. citizens for research abroad. Expansion of the training of foreign nationals in the United States from about 90 per year to about 150 per year is proposed. This will require an increase in the funds devoted to the highly productive foreign fellowship program from $500,000 to a level of $1,200,000. This program is financed from funds appropriated to the Division of General Medical Sciences.

In connection with the training of U.S. citizens to conduct research abroad, the Nation faces continuing and growing needs to staff a variety of vital research operations outside the United States. Both to staff these currently and to build a strong group of competent investigators with research interests centered outside the United States, special training efforts are indicated. This can be done by providing funds available for the training of scientists at pre- and postdoctoral levels, concentrating upon the postdoctoral in laboratories operated by the United States in other countries. To initiate such a program funds to support about 20 trainees would be adequate. The total cost would approximate $200,000, and the program would be administered by a part of the direct operations of the National Institutes of Health.

PART C. REVISED NIH PROPOSAL FOR TRAINING AND FELLOWSHIPS FOR FISCAL YEAR 1963

Combining the NIH proposal presented in part A with the modifications outlined in part B produces the budget proposal stated on the following page:

Institute	Amounts (in thousands)		Increase	
	President's budget	Revised, National Institutes of Health	Amounts (in thousands)	Percent
Total	$145,746	$177,500	$31,754	21.8
Fellowships	25,996	31,580	5,584	21.5
Training	119.750	145,920	26,170	21.9
Division of General Medical Sciences	40,397	51,000	10,603	25.0
Fellowships	10,997	11.980	983	4.4
Training	29,400	39,020	9,620	32.7
National Cancer Institute	10.880	13,400	2,520	23.2
Fellowships	3,100	3,400	300	9.7
Training	7,780	10,000	2,220	28.5
National Institute of Mental Health	47,542	52,000	4,458	9.4
Fellowships	2,892	4,740	1,848	63.9
Training	44,650	47,260	2,610	5.8
National Heart Institute	14,154	17,666	3,512	24.6
Fellowships	3,615	4,450	835	23.1
Training	10,539	13.216	2,677	25.4
National Institute of Dental Research	4.623	6.600	1.977	42.8
Fellowships	882	1,230	348	39.5
Training	3,741	5,370	1,629	43.5
National Institute of Arthritis and Metabolic Diseases	10,702	14,334	3,632	33.6
Fellowships	1,177	1,800	623	52.9
Training	9,525	12,534	3,009	31.5
National Institute of Allergy and Infectious Diseases	6,960	9,100	2,140	30.7
Fellowships	1,610	1,900	290	18.0
Training	5,350	7,200	1.850	34.6
National Institute of Neurological Diseases and Blindness	10,488	13,400	2,912	27.8
Fellowships	1,723	2,080	357	20.7
Training	8,765	11,320	2,555	29.2

In addition to that proposal, $200,000 will be required for the direct operations budget of NIH to finance the new program for direct traineeships for pre- and post-doctoral trainees to work in U.S. laboratories outside the United States.

When the proposed budget is viewed functionally by program rather than in terms of Institute budgets, the situation would be as follows:

Program	Amount (in thousands)	Percent increase over President's budget
Total	$177,500	21
Fellowships	31,580	21
Predoctoral	4,578	23
Postdoctoral	8,731	15
Special	2,470	14
Career	14,601	24
Foreign	1,200	71
Training	145,920	21
Undergraduate	17,867	20
Graduate	128,053	21

DEVELOPMENT OF 1963 BUDGET

Mr. FOGARTY. Were any of these deficiencies apparent last September?

Dr. SHANNON. Some of them were, Mr. Chairman. We were aware that we were not using the fellowship devices as extensively or as productively as we could.

Mr. FOGARTY. You asked for more money than you received, didn't you?

Dr. SHANNON. Yes, sir.

Mr. FOGARTY. Do you want to say anything about that? Do you think the need is still there? It must be, in view of this report.

Dr. SHANNON. It is still there, Mr. Fogarty.

Mr. FOGARTY. What was the original request in this area?

Dr. SHANNON. The Institutes requested, in the aggregate, for fellowships, $45 million; for training, $166 million. We felt that we were unable to support their requests to that extent, but we did request $31 million in fellowships, and $136 million in training grants. This was an increase of about $21 million over and above the ongoing programs.

We felt that that was as far as we could go on the basis of the solid information we had last September.

Mr. FOGARTY. Then what happened?

Dr. SHANNON. We were allowed to continue at the 1962 program level, with the exception that we were permitted to increase mental health training by about $10 million.

At that time we had the manpower study underway, and the Bureau of the Budget was unwilling to commit itself to any increase until the study was completed.

Mr. FOGARTY. You have this study completed now, and you are going to bring these recommendations up to date.

Dr. SHANNON. This we shall be glad to do.

CURRENT MECHANISMS FOR TRAINING SCIENTISTS

Mr. Fogarty. Would you care to make any general comment on the adequacy of the present mechanisms available for training scientists?

Dr. Shannon. Yes, sir; I should like to comment on that. I am not convinced that we need new legal authority. But I do think that our present mechanisms tend to diffuse activity in the schools so that it is difficult to develop the optional environment for training scientists most advantageously.

We have seven Institutes and one Division, and in consequence we run training programs out of eight accounting points.

Within any one of the eight appropriations we may have as many as 8 or 10 programs. So we may have at the NIH about 80 discrete training programs—each as a special training program in itself, though they do operate under common guidelines.

When an institution decides, as a matter of policy, to expand the opportunities it offers for the training of scientists, there is no central point within the NIH to which it can turn with a view to developing a logical sequence of actions that will result in a broad graduate education program in the sciences.

The school must depend upon individual scientists to make independent application via several of the training groups within the Institutes, and then attempt, after this has been done successfully in a number of areas, to put an institutional training program together.

This usually does not result in a well-balanced training educational experience within the universities. For example, most of the biologists we train should have a broader experience in mathematics than they are getting at the present time.

If a school has a training grant in cardiovascular disease and another training grant in cancer and another one in arthritis, it has certain responsibilities to the Training Committees in the Institutes from which the funds are derived. It is very difficult for any central authority to provide the general background and fundamental training, that is required in each of these areas.

On the other hand, if as a matter of policy, the institution decides that it is going to organize a more orderly program of science education in order to develop a strong graduate curriculum in the sciences we do not have any simple mechanism within our programs that would help them to plan, finance, and conduct that type of operation.

GENERAL NIH GRANTS

We have now suggested to several institutions that they make concrete proposals to us showing how they would handle the bulk of graduate science education within their institution if it were possible to do this under some sort of a single general grant. We will take such general requests if they evaluate, break them down into categorical pieces and see whether, after intercouncil consideration of the totality, the institution can receive a broad general commitment.

In general, the training programs in the institutions are currently determined by the individual applications of a professor or an associate professor and, as a result of that, by the individual actions of training committees of one or more of our institutes.

I think this was fine during the early stages of development of the program, but I think the training program is now so broad that other devices of a more general nature must be introduced. If we find we cannot do it within the framework of current legislative authority, then we shall discuss with the Public Health Service the possibility of asking for broader authority.

TRAINING AUTHORITY

We know that we have the basic authority in the general research and training grant program, but this has a limitation of 15 percent of the research grant funds. If we atempted to do any substantial amount of training under that authority, we would not have adequate funds.

So, unless we can develop a technique for handling broad problems through the joint actions of several institutes, we shall probably have to request some new authority or some easement of the 15-percent limitation on the general authority.

The general authority was not meant specifically for this purpose, so that its use as a broad training support mechanism would have to be defended right from the beginning.

1963 BUDGET FOR TRAINING

I do feel that our expenditures in training, which this year will be $145 million——

Mr. Fogarty. Are you talking about 1962, now?

Dr. Shannon. 1963, sir. It will be $145 million if one includes the $25 million in fellowships. With the expenditure of money at that level, we should now begin to develop total graduate academic environments and not try to develop the total program as a series of individual, unrelated, or only partially related programs.

Mr. Fogarty. What did you ask the Bureau of the Budget compared to that $145 million?

Dr. Shannon. $167 million.

Mr. Fogarty. A cut of $22 million.

Mr. Seggel. Yes, sir.

Mr. Fogarty. Do you still think that could be used to advantage?

Dr. Shannon. I think so, yes.

SCIENTIFIC PERSONNEL RECRUITMENT

Mr. Fogarty. What kind of a recruitment program do you have?

Dr. Shannon. Mr. Fogarty, this would be one of the major functions of the expansion of the predoctoral fellowship program I discussed before. For example, if one were going to bring predoctoral fellows into the medical school to work toward a combined M.D.-Ph. D. degree—or an M.D. degree for medical research rather than for practicing medicine—I think one would go to the colleges and attempt to get people who were broadly based in the physical sciences rather than individuals who were taking the routine premedical course.

In precisely the same way, if one expanded the predoctoral fellowships in the Ph. D. program, one would attempt to recruit people from the physical as well as the biological behavioral sciences, people who were majors in mathematics or majors in physics, for example.

Recruitment, in the absence of the ability to support the individual, is not a very profitable thing to undertake at a time when individuals can receive total support in their science training in the physical sciences. They can be assured careers in the physical sciences.

I should like to emphasize at this point that I believe subsidy of the individual during the early years of his scientific training is essential if we are to capture for science a reasonable proportion of the better minds.

What we have to do in biology and medicine is to provide career opportunities and career stability at least equal to that in the physical sciences.

VIEW OF MEDICAL SCHOOL DEANS

Mr. Fogarty. With regard to the training grant area, are you satisfied that you have straightened the record out as far as the deans of the medical schools are concerned, and satisfied their complaints which they have been writing to me about for the past year?

Dr. Shannon. Mr. Fogarty, I have tried to make our point of view quite clear. The thing is, there is a fundamental difference of opinion between ourselves and some of the deans.

Mr. Fogarty. I have received a lot of letters.

Dr. Shannon. Yes, sir.

Mr. Fogarty. I sent some out to you.

RESIDENCY TRAINING

Dr. Shannon. I think that most of the deans would be very happy with the program we propose for 1963. I think some of the deans who feel that the NIH should accept a much broader responsibility for residency training will not be satisfied.

But we are not recommending that because we feel that the problem of residency training relates more to the practice of medicine than to research and is part of the complex of factors in general aid to medical education and general aid to the development of medical specialists.

If the Public Health Service is to proceed into this area in a substantial way, then it is our feeling it should be by our new Bureau of Community Services. I think Dr. Terry may want to comment on that.

Mr. Fogarty. Doctor?

Dr. Terry. This is a matter which we have had under some consideration and discussion in relation to the need for training of many of the people who would subsequently be clinical investigators or teachers. It would therefore supplement the academic needs of our expanding medical education program.

As you know, we have thus far supported a residency type of training in certain of the sharply circumscribed specialties such as mental health, neurological disease, and ophthalmology. There is a strong feeling on the part of the people in the medical schools and related positions throughout the country that some sort of similar support is needed for training of the man in a residency in internal medicine, because generally speaking, those programs are the ones which produce the man who is going to be professor of medicine and the head of a department.

They produce the coming academic people in the fields of less sharply circumscribed specialties. I am referring to specialties such as surgery, internal medicine, obstetrics, gynecology, and related areas.

The basic problem, of course, in this respect is related to the thing that Dr. Shannon pointed out earlier, and that is that most of the residency training programs in these areas—at least today—are directed more toward making the medical specialist practice medicine.

It is true that the cream of the graduates going through those programs do go into the academic field and do become the big contributors in teaching, clinical research, and so forth. I think that quite obviously, though we have not reached the final decision on it, we have discussed it a great deal.

Just within the past month I have had a special meeting with the National Advisory Health Council discussing this specific factor. I don't think at this stage we are in any position to make a specific recommendation related to this particular point.

But I do think that in general I would agree with Dr. Shannon that, if these programs are to be supported, they should be redesigned in such a way that they would in effect add the various aspects of clinical research, academic medicine, and this sort of thing, which would in effect prepare the people for the thing that we are talking about.

In other words, we feel that if we are to support the training of these people, they should purposely be trained for certain key positions such as this, rather than accidentally turn out to be that.

I think, too, that if such training is planned far in advance and the research and related types of disciplines are the disciplines that would contribute to making this person a potential research worker as well as a fine doctor, that we very well may be able to shorten the length of the overall training that is required for that individual today.

For instance, Dr. Shannon mentioned a moment ago that a man who goes through a residency training program may, after his internship, spend 3 or 4 years in such training. Then, at the end of that time, generally speaking, if he is going to be a well-qualified research worker, even in the fields of clinical research, it often requires an additional year plus, up to 2 or 3 years, for him to get the training in some of the special disciplines that he needs.

So the major thing that I would like to say in that respect is that we are discussing this freely with our advisers. We are aware of needs in this direction. But, as of today, we do not have the proposal to present to you which we feel is sufficiently sound and complete to expect your support.

Mr. Fogarty. We are going to get that in a couple of weeks?

Dr. Terry. No, sir; we won't have this in a couple of weeks. I think if we have it by next year we will be doing good, Mr. Chairman.

The thing that Dr. Shannon is talking about in terms of expanding the areas in which we are already operating——

Mr. Fogarty. I understand.

Dr. Terry. Will be available within a couple of weeks.

Dr. Shannon. There is another thing, Mr. Fogarty. This problem cannot be resolved without knowing whether there will or will not be general support for medical education. The best way to provide the general backdrop for sound education in medicine, whether for service or for science, is to have stronger institutions, which means subsidy of medical schools by some device.

I think until the schools themselves are on a more solid financial base, the type of problem that Dr. Terry just talked about will always be before us and we will be unable to resolve it adequately within one specific set of authorities such as we have.

PROFESSIONAL JUDGMENT BUDGETS FOR EACH INSTITUTE

Mr. FOGARTY. A few days ago I asked our clerk to tell Mr. Kelly that I would expect each Institute Director to prepare a budget reflecting what in his professional judgment should be appropriated for 1963. I assume this information was passed on to you?

Dr. SHANNON. Yes, sir.

Mr. FOGARTY. May we have that now so we can put it in the record in one place, Institute by Institute?

Dr. SHANNON. Yes, sir.

Mr. FOGARTY. We will put them in the record.

(The requested information follows:)

SUMMARY OF PROFESSIONAL JUDGMENT BUDGETS SUBMITTED BY NIH INSTITUTE DIRECTORS

The Directors of the several Institutes and Chiefs of the program Divisions of the National Institutes of Health have submitted estimates for 1963 which reflect in their best professional judgment the total funds which could be used for their individual programs.

These estimates have not been influenced by the Office of the Director, National Institutes of Health, the Office of the Surgeon General, or the Office of the Secretary through guidelines or review such as normally occur in the budgetary process. They do not, therefore, represent in the aggregate an NIH budgetary proposal. Consideration has not been given to those factors which normally influence budget proposals, such as—

1. The consistency of the proposals of individual Institutes with existing congressional directives and legislation.
2. The appropriateness of relative emphasis among programs as for example between research grants and training grants.
3. The adequacy of manpower, space, and other resources when the total budgets of all Institutes are added up.
4. The effect of combined Institutes' proposals upon educational institutions.
5. The sum total of all proposals in relation to fiscal feasibility and other broad policy considerations.
6. The effect of projected program increases upon the central (NIH) management requirements.

GENERAL RESEARCH AND SERVICES

Comparison of 1963 President's budget with 1963 professional judgment budget estimate

[In thousands]

	1963 President's budget	Professional judgment budget estimate	Increase
Grants and related contracts:			
Research	$100, 409	$126, 280	$25, 871
Fellowships	10, 997	18, 000	7, 003
Training	29, 400	45, 000	15, 600
Total, grants and related contracts	140, 806	189, 280	48, 474
Direct operations:			
Biologics standards	4, 000	4, 000	0
Review and approval	2, 379	2, 736	357
Administration	641	704	63
Total, direct operations	7, 020	7, 440	420
Total estimate	147, 826	196, 720	48, 894

1. Research and related contracts, increase of $48,474,000

A. Research grants, increase of $25,871,000

1. Regular program, increase of $16,871,000:

1962 program	$42, 529, 000
1963 continuations (type 5's and 2's)	36, 150, 000
Backlog of approved but unpaid applications, end of fiscal year 1962	2, 055, 000
1963 supplements	3, 400, 000
1963 new projects	28, 835, 000
Total need for 1963	70, 440, 000

At the close of 1962 it is predicted that there will be a backlog of approved but unpaid research projects approximating $2,055,000. On the basis of experience from the past several years it may be predicted that regular new grant applications recommended for approval by the advisory groups will reach at least $28,835,000 for 1963, an increase of 20 percent minimum in new applications over 1962.

These increases will be devoted primarily to fundamental biomedical research in such fields as biochemistry, genetics, cell biology, physiology, embryology, and development, to public health problems, including nursing and epidemiology, and to projects in allied fields. In addition, emphasis will be directed toward a number of emergent research areas warranting increased consideration because of their pressing and timely importance to the development of contemporary biology and medicine. These include studies of aging, biomedical engineering, histocompatibility, research in comparatve anatomy, developmental biology, and projects which are relevant to several of the categorical institutes and the Division of General Medical Sciences.

Increased emphasis will also be placed on basic research in the behavorial sciences. Support of the emerging sciences of biocybernetics and psychophysics will lead to exact knowledge of mental and behavioral processes as studied by mathematical and physical methods.

Additional support of basic research on animals in marine environments will offer research opportunities not available in terrestial forms of life.

This projected requirement represents an increase of $16,871,000 over the 1963 President's budget.

2. General research support grants, no increase.

3. General clinical research centers, increase of $4 million:

1962 program	$27,000,000
1963 commitments	19,400,000
Backlog of approved but unpaid applications, end of fiscal year 1962	2,500,000
1963 supplements	3,200,000
1963 new projects	12,400,000
Total need for 1963	37,500,000

At the close of 1962 the blacklog of approved but unpaid general clinical research center applications will be approximately $2,500,000. The total of committed continuations, estimated supplements, and the backlog as of June 30, 1962, would bring the level of the program to $25,100,000.

The $12,400,000 will permit the establishment of 24 new clinical research centers in leading medical schools and research hospitals. There is urgent need for increased investigation of human diseases by direct research on patients under scientifically controlled and safe conditions. These new centers will also permit the accelerated investigation of the applicability of results from laboratory and animal research to the diagnosis and treatment of human disease.

4. Special research resource centers, increase of $5 million:

It is estimated that $10 million, an increase of $5 million over the 1963 President's budget, will be required to meet the large and present need for special research resource centers. On the basis of presently expressed interest approved applications and those pending review it appears that the principal need is for support of biomedical computer research resources.

In addition to the support of biomedical computer research resources, support of research resources will be provided in biomedical electronics and biomedical engineering, central pathology resources, and central isotype laboratories.

B. Fellowships, increase of $7,003,000

1962 program		$10,997,000
1963 increases:		
Regular fellowship program:		
Predoctoral	$2,300,000	
Postdoctoral	1,600,000	
Special	553,000	
Subtotal	4,453,000	
Research career award program (including development awards)	2,000,000	
Foreign	550,000	
		7,003,000
Total need for 1963		18,000,000

Additional funds for this program will be used to expand the opportunities for intensive research training of candidates in the fundamental biomedical and other health-related sciences in such shortage areas as medical genetics, physiology, molecular biology, and experimental pathology.

The total requirements estimated for 1963 of $18 million represent an increase of $7,003,000 over the 1962 program of $10,997,000. Approximately $8,527,000 is required for the regular fellowship program to support increased numbers of candidates and to encourage others in future years to elect careers in the fundamental fields of the biological sciences. An additional $2 million is requested for the research career award program, bringing the total annual support of this program to $8,223,000. This will permit the continued growth of this successful program in 1963 and help provide increased numbers of stable career opportunities for scientists of superior potential and capability in the basic sciences related to health. Approximately 100 new awards can be made in 1963 with this increase.

In the foreign fellowship program, an increase of $550,000 is requested, bringing the total support to $1,250,000, which will support about 141 foreign nationals.

C. Training, increase of $15,600,000

1962 program	$29, 400, 000
1963 commitments	29, 400, 000
Approved but unpaid applications end of fiscal year 1962	4, 500, 000
1963 new projects	11, 100, 000
Total need for 1963	45, 000, 000

The total requirements for 1963 of $45 million represent an increase of $15,600,000 over the 1963 President's budget of $29,400,000. This increase is based upon the estimated need as developed in the studies done by the NIH for the House and Senate Appropriations Committees. In view of the number of high-quality applications received from basic science departments of the medical and graduate schools and recommended for support by training committees composed of non-Federal experts in the basic science fields and the National Advisory Health Council, the proposed increase is realistic.

At the end of 1962, it is estimated that approximately $4,500,000 of approved applications cannot be paid from 1962 funds. The $11,100,000 for new projects in 1963 represents estimated approvals of $6,500,000 in research training grants, $1,800,000 for continuation and expansion of current medical student research training programs, and $2,900,000 for initiation of wholly new programs.

The increase in research training grants will be used largely to give emphasis to the areas of (1) biophysical sciences, (2) developmental sciences, (3) biomathematics, (4) biomedical engineering, (5) comparative pathology, and (6) the basic behavioral sciences.

2. Direct operations, increase of $420,000

A. Biologics standards, no increase

B. Review and approval, increase of $357,000

An increase of $357,000 and 38 additional positions will be required to administer the expanded noncategorical research grants program and research training programs.

C. Administration, increase of $63,000

An increase of $63,000 and seven positions will be required for the overall planning, direction, and coordination of the programs of the Division of General Medical Sciences.

CANCER INSTITUTE

Comparison of 1963 President's budget with 1963 professional judgment budget estimate

[In thousands]

	1963 President's budget	Professional judgment budget estimate	Increase
Grants:			
Research	$65,830	$65,830	0
Fellowships	3,100	4,880	$1,780
Training	7,780	11,470	3,690
State control programs	3,500	3,500	0
Community demonstration projects	4,000	4,000	0
Total grants	84,210	89,680	5,470
Direct operations:			
Research	16,038	17,293	1,255
Collaborative studies [1]	34,341	45,272	10,931
Professional and technical assistance	1,836	1,836	0
Review and approval	1,735	1,962	227
Administration	949	1,057	108
Total direct operations	54,899	67,420	12,521
Total estimate	139,109	157,100	17,991

[1] Principally research contract funds.

1. Research and related activities, increase of $5,470,000

A. Research grants

The President's budget contains ample funds for research grants in this activity. However, as time has passed it appears that certain of the program segments will require more funds and others less than that indicated in the budget. For example, it now appears probable that certain clinical programs can best be financed through regular projects and programed chemotherapy grants rather than as centers. The ability to shift funds freely is essential if we are to avoid holding back important programs for lack of funds, while other programs have more funds than our ability to launch them warrants.

B. Fellowships, increase of $1,780,000

1. Postdoctoral and special fellowships, increase of $500,000: An increase of $500,000 to cover the 70 additional candidates expected to be recommended and for which the budget does not provide sufficient funds would be a sound investment.

2. Research career development awards, increase of $1,280,000: The number of well-qualified candidates nominated for these junior awards next year are expected to increase and provide a real opportunity to accelerate the career development of promising young scientists. An increase of $1,280,000 would permit 65 new awards over and above the 15 existing awards which will cost $220,000 to continue.

C. Training, increase of $3,690,000

1. Undergraduate training grants: The National Advisory Cancer Council has consistently recommended that funds for this activity be increased to restore them in terms of purchasing power to a status more in line with that of 10 years ago. Payments to schools have been held constant since that time.

No increase over the President's budget is recommended because of pending legislation for aid to medical education. If this legislative proposal is not enacted I would recommend an increase of $2,085,000 in this subactivity to permit payments of $40,000 to 4-year schools, $25,000 to 2-year schools, and $10,000 to dental schools.

2. Graduate training grants, increase of $3,690,000: For continuation of graduate training grants awarded in 1962, $5,300,000 will be required. Expansion of current training programs in certain special areas would require $600,000 for supplemental grants. New training programs in the general fields pertinent to

research but with special emphasis of program interest in cancer include epidemiology, toxicology, pharmacology, carcinogenesis, and special diagnostic areas such as laboratory medicine and clinical pathology. Estimated costs of such programs is $1,600,000. Training program in radiation therapy, radiation physics and chemistry, and radiation biology would utilize $1,490,000 for new grants to begin in 1963. Although there is general agreement that the need for training in these areas would require funds in greater amounts than those shown here, ability to mount increased training programs makes these proposed increases more realistic.

2. Direct operations, increase of $12,521,000

A. Research, increase of $1,255,000

1. Direct program, increase of $658,000: I have reported on recent advances in surgery research—e.g., combined surgery and chemotherapy in breast cancer. With completion of the new surgery suite, space is available to expend our surgical program. We would propose to increase the surgery staff, provide laboratory animal caretakers for experimental surgery, and establish an intravenous therapy team.

We should also strengthen our radiation research and intensify cooperative research with Public Health Service hospitals in chemotherapy programs. The use of computers in solving basic research problems is a research area that offers considerable profit.

2. Payment to NIH management fund, increase of $597,000: Reimbursements to the NIH management fund (see also "Review and approval" and "Administration" items) are all estimated on the basis of the same ratios shown in the President's budget.

B. Collaborative studies, increase of $10,931,000

1. Field studies, increase of $2,178,000: Planned programs could soundly use increases of $1,005,000 for diagnostic contracts and $300,000 for direct operations.

These increases would be used for expansion of laboratory medicine activities to increase the degree of reliability of clinical laboratory methods through automation; the development of inbred rabbit lines for use of immunologists in securing more uniformly interpretable biological reactions; and for acquiring new information and improved diagnosis during surgery through techniques in TV radiology.

Increases totaling $390,000 would be used as follows: (1) End results: $200,000 in biometry contracts and $100,000 in direct operations for additional end results studies growing out of expanded clinical trials. These studies of therapy evaluation concerning cancer mortality and survival from treatment will be extremely valuable to cancer research investigators internationally. The end results program aids physicians in determining most effective courses of treatment. (2) Other biometry activities: $55,000 in contracts and $35,000 in direct operations for additional development of new mathematical and statistical approaches to comparative cancer incidence studies, an important approach to problems of cancer etiology.

Increases of $200,000 for epidemiology contracts and $25,000 for direct operations would be used for the following: (1) Veterans' Administration study on the relationship of cancer to various antecedent medical findings. The Veterans' Administration has extensive information on World War I and II veterans that could be a principal part of cancer epidemiological studies. (2) Expansion of animal tumor diagnostic facilities for epizoology studies and development of a system for collection of veterinary medical data which can be used for individual and collaborative studies of chronic diseases in animals. These investigations would endeavor to show the relationship between natural cancers of man and those in animals.

An increase of $258,000 would be used for contracts to develop new and better methods of testing for cancer-causing agents. New methods are urgently needed to lessen the time it takes to determine whether a particular agent is involved in causing cancer.

2. Cancer chemotherapy activities, increase of $4,875,000: Increased funds could well be used in pharmacology studies of drugs indicating promise for use in man. Studies of tumor tissue would also be undertaken. Additional genetic breeding and disease control centers would be established to provide increased numbers and variety of high quality research animals. Expanded studies in the clinic for followup of new leads and for the definitive evaluation of drugs

requires increased preparative laboratory facilities to provide the large quantities of materials needed; and correspondingly increased emphasis on pharmacological and toxicological studies and pharmacological preparation of materials for clinical usage. Greater attention will be focused on studies in human tumor biochemistry to obtain information of critical value to the clinician in the selection of chemotherapy agents.

3. Cancer virus activities, increase of $3,878,000: An increase of $3,778,000 for contracts and $100,000 for direct operations would provide materials and information critically needed in the cancer virus research laboratories which will be the selection and development of defined research animals; development of rapid viral identification methods; carcinogenesis screening; and virus research centers.

C. Review and approval, increas of $227,000

The expanded activities covered above would require additional moneys for the necessary expanded review and approval functions.

D. Administration, increase of $108,000

The expanded activities covered above would require additional moneys for the necessary expanded administration functions.

MENTAL HEALTH

Comparison of 1963 President's budget with 1963 professional judgment budget estimate

[In thousands]

	1963 President's budget	Professional judgment budget estimate	Increase
Grants and related contracts:			
Research	$54,437	$63,145	+$8,708
Fellowships	2,892	7,000	+4,108
Training	44,650	53,000	+8,350
State control programs	6,750	15,000	+8,250
Total grants and related contracts	108,729	138,145	+29,416
Direct operations:			
Research	9,775	11,134	+1,359
Collaborative studies	2,573	3,058	+485
Training activities	596	596	--------------
Professional and technical assistance	2,122	3,572	+1,450
Review and approval	2,413	3,549	+1,136
Administration	691	691	--------------
Total direct operations	18,170	22,600	+4,430
Total estimate	126,899	160,745	+33,846

I. GRANTS AND RELATED CONTRACTS, INCREASE OF $29,416,000

A. Research grants, increase of $8,708,000

1. Regular program, increase of $6,708,000.
2. Categorical clinical research centers, increase of $2 million.

B. Fellowships, increase of $4,108,000

C. Training, increase of $8,350,000

D. State control programs, increase of $8,250,000

II. DIRECT OPERATIONS, INCREASE OF $4,430,000

A. Research, increase of $1,359,000

B. Collaborative studies, increase of $485,000

C. Professional and technical assistance, increase of $1,450,000

D. Review and approval, increase of $1,136,000

I. GRANTS AND RELATED CONTRACTS

A. Research grants, increase of $8,708,000

Projection of recommended grants:

1. Continuations and supplementals	$35, 500, 000
2. New grants including carryover	19, 380, 000
3. Indirect costs effective Jan. 1, 1963	1, 320, 000
4. Subtotal	56, 200, 000
5. General research support grants	3, 900, 000
6. Categorical clinical research centers	3, 000, 000
7. Scientific evaluation and planning	45, 000
Total research	63, 145, 000

1. *Regular program*—Of the total of $56,200,000 for the core programs, $31,700,000 is for the regular programs, $13 million, for the psychopharmacology programs, and $11,500,000 is for the mental health project grants (title V) program.

2. *Categorical clinical research centers.*—These research centers have proven effective; and the growth of this program will be substantial.

B. Fellowships, increase of $4,108,000

Program analysis:

1. Predoctoral	$3, 150, 000
2. Postdoctoral	1, 250, 000
3. Special	750, 000
4. Research career awards	650, 000
5. Career development awards	1, 200, 000
Total fellowships	7, 000, 000

The increases in this program would permit it to gain ground on the greatly expanded research programs which require ever greater numbers of trained mental health researchers. A significant percentage of the increase would permit payment of approvals unpayable in 1962. Career development awards, an adjunct to research career awards, would have a major increase in order to support and encourage the promising, younger researcher.

C. Training, increase of $8,350,000

Program analysis:	
Undergraduate	$5,750,000
Graduate:	
General practitioner	6,000,000
Research training	7,000,000
Special areas	2,000,000
Pilot projects, institutes, and conferences	3,000,000
Regular program	26,250,000
Subtotal graduate	44,250,000
Special inservice training	3,000,000
Total training	53,000,000

These increases would permit a level of support sufficient to relieve the serious needs within the existing program. For instance, additional efforts would expand mental health research training in the behavioral sciences. Sufficient additional funds are needed to initiate new areas of support. Notable in this latter respect would be the special inservice training programs. The final report of the Joint Commission on Mental Illness and Health stressed this type of training program. Funds could be made available to various State and local hospitals and agency facilities to support, on a demonstration basis, training programs for a wide range of mental health personnel. These would include psychiatric aids, occupational therapists, recreational therapists, as well as persons within the core mental health professions who are pursuing inservice training to improve their professional qualifications.

D. State control programs, increase of $8,250,000

This increase would permit a first step toward implementation of the final report of the Joint Commission on Mental Illness and Health within the limits of section 314(c) of the Public Health Service Act. Programs could be mounted with particular attention being paid to broad-gaged community mental health programs such as day hospitals, night hospitals, community mental health clinics for both children and adults, clinics for the mentally retarded, aftercare, intermediate care, and rehabilitative services, general hospital psychiatric units, and intensive psychiatric treatment centers.

II. DIRECT OPERATIONS

A. Research, increase of $1,359,000

1. *Multidisciplinary study.*—An increase of $75,000 would provide for a multidisciplinary study in schizophrenia directed toward a detailed psychological, physiological, and physical study of monozygotic twin pairs in which one twin has schizophrenia and the other does not, and their families.

2. *Cross-cultural studies.*—An increase of $50,000 would provide for cross-cultural studies in order to increase our knowledge of normal human development, mental illness and treatment in terms of the relationship between social factors and mental illness in cultures which differ from our own.

3. *Addiction Research Center.*—An increase of $70,000 would permit the transfer of the Navy-reimbursed part of the center budget ($50,000) to the Institute budget in order to eliminate a scientific and administrative risk and burden; and, secondly, it would provide additional care for animals when the animal research building is completed in the spring of 1963.

4. *Neuropsychology.*—An increase of $34,000 would provide for training and testing animals and for increased utilization of electronic equipment.

5. *Telemetering and remote stimulation.*—An increase of $200,000 would permit the development of a telemetering device to telemeter EEG, heart rate, and respiration. Available devices can telemeter only one of the above variables at a time presently. This increase would also be utilized to develop a remote stimulator which would be quite small and sensitive enough to trigger receiving equipment at a distance.

6. *Office of the Associate Director for Intramural Research.*—An increase of $300,000 would provide $250,000 for replacement of deteriorated and obsolete equipment, for purchase of new equipment and for increased costs of data-processing equipment and programing services. This increase would also provide

needed positions in the Laboratory of Neurophysiology and for technical development.

7. *Information.*—An increase of $80,000 would permit a greater dissemination of information.

8. *NIH management fund.*—An increase of $550,000 would be used for centrally furnished research services.

B. Collaborative studies, increase of $485,000

1. *Professional services.*—An increase of $100,000 would facilitate development activities.

2. *Biometrics.*—An increase of $75,000 would permit the financing of increased costs of data-processing and programing services.

3. *Mental Health Study Center.*—An increase of $90,000 would permit the center to prepare a bibliography on adolescent behavior, to formulate a family classification system and to collect baseline data from community agencies.

4. *Office of the Associate Director for Program Development.*—An increase of $20,000 would permit this Office to carry out its increased responsibility for coordination of program development.

5. *Psychopharmacology Service Center.*—An increase of $200,000 would permit the center to expand its activities in the area of exchange of scientific information by scientists and practitioners in the vast and complex field of psychopharmacology.

C. Professional and technical assistance, increase of $1,450,000

1. *Community services.*—An increase of 32 positions and $1,250,000 would permit this program to expand services to State and local communities as recommended by the final report of the Joint Commission on Mental Illness and Health. Consultation, for instance, is given in a variety of areas; e.g., school mental health, mental retardation, aging, alcoholism. Professional assistance is given to grantees of mental health project grants. This program is administered in this activity. Technical assistance projects, demonstrations, and pilot projects to State and local mental health agencies would be increased ($900,000) as part of the program to bridge the gap between research discoveries and their utilization. These projects will aid States in the implementation of the Joint Commission report. Demonstrations and pilot projects would be expanded and might include demonstrations of psychiatric alternatives to State hospital care, pilot programs in prenatal clinics, well-baby clinics, visiting nurses, day-care centers and nursery schools for early intervention into emotional disturbances, a demonstration of program analysis in a State mental health program, and special projects in mental retardation, brain-damaged children, alcoholism, narcotic addiction, and juvenile delinquency.

2. *Regional staff.*—An increase of $200,000 would provide for expansion of the regional staff. It is through these staffs that the Institute provides direct technical assistance to State governments and State and local organizations. These staffs must be increased if the Institute is to meet the rising demand for professional assistance in all areas of mental health.

D. Review and approval, increase of $1,136,000

1. An increase of $700,000 would provide additional staff to administer the greatly increased research and training grant programs. Further, the increase would provide for extension in the program analysis staff.

In meeting the concern expressed by the Congress as well as many leaders in the field of mental health, the Institute is in the planning stages for an extensive program analysis and communication of research findings functions. While the Institute has always devoted significant effort to this area, it is evident that with the ever-increasing flow of information emanating from research and training activities as well as from operational programs, that major steps must be taken to insure the full utilization of this information. The increases provided would permit the first steps to be taken in this area.

2. An increase of $436,000 would permit payment to the NIH management fund for centrally provided review and approval services.

HEART

Comparison of 1963 President's budget with 1963 professional judgment budget estimate

[In thousands]

	1963		Increase
	President's budget	Professional judgment budget	
Grants and related contracts:			
Research	$89, 720	$95, 800	$6, 080
Fellowships	3, 615	5, 900	2, 285
Training	10, 539	15, 000	4, 461
State control programs	5, 000	7, 000	2, 000
Total, grants and related contracts	108, 874	123, 700	14, 826
Direct operations:			
Research	9, 985	10, 100	115
Collaborative studies	1, 330	1, 330	0
Training activities	186	300	114
Professional and technical assistance	4, 111	4, 711	600
Review and approval	1, 958	2, 200	242
Administration	454	500	46
Heart Gerontology Building	380	380	0
Total, direct operations	18, 404	19, 521	1, 117
Total estimate	127, 278	143, 221	15, 943

EXPLANATION OF INCREASES

1. Grants and related contracts, increase of $14,826,000

A. Research grants, increase of $6,080,000

1. Regular program, increase of $4,080,000: The greater part of this increase, about $2,680,000, would be applied to continuation and supplemental requirements in the budget year. Although the continuation estimate shown in the President's budget would indicate a decrease in 1963 from the experience ratio used in previous years, it is becoming apparent that the reverse is actually true. There are several factors which are contributing to an upward trend in the overall continuation. One of these factors is the inclination of the Advisory Council to support new investigators on a limited basis, with a commitment either expressed or implied for increased support in the following year if the later review indicates that it is warranted. Another is the natural consequence of the program which is designed to expand the available resources for categorical clinical research. As cited in the President's budget narrative, the broad-scale research programs which relate to and utilize these facilities must be given assured support for longer terms than the individual projects receive, to attain maximum stability for the research and the research personnel.

Approximately $400,000 of the increase would be needed for support of additional program projects related to the expanded clinical research facilities. The balance of $1 million would be utilized for mounting pilot studies leading toward comparison of drugs for prophylaxis of atherosclerosis in collaborative studies, and to implement feasibility studies for large-scale testing of dietary programs.

2. Primate centers, increase of $2,000,000: Two years of developing this program have shown that estimates for operating these centers should have included some provisions for a cost escalator in the course of initial staffing, stocking, and moving toward full-scale operation. Current estimates indicate that the requested increase would provide the needed flexibility in 1963 and subsequent years for maintenance of seven centers—four regional centers initiated in 1961 and two regional centers and a conditioning center being established in 1962.

B. Fellowships, increase of $2,285,000

The requested increase would provide for support of 143 additional postdoctoral fellowships, 21 additional special fellowships, and 60 additional career and career-development awards, for a total of 621 awards in 1963. This is the first-year target of the 5-year projection report of December 25, 1961, which outlines the need for trained persons and the proposed means to fulfill the need.

C. Training grants, increase of $4,461,000

This increase would provide $1,365,000 for raising the base grant in the undergraduate program—for 4-year schools of medicine and osteopathy from $25,000 to $40,000, and for 2-year medical schools from $15,000 to $25,000. It would also provide $25,000 for the inclusion of one new 2-year school. The balance of $3,071,000 will provide for strengthening existing programs and mounting of additional programs for training in areas of need. About 75 new programs and 200 additional trainees will be supported.

D. State control programs, increase of $2 million

As pointed out in the President's budget, each dollar placed in this formula elicits from the States a matching dollar which is used directly for prevention and control of heart diseases. Present knowledge indicates that there exists in communities and localities throughout the States many more opportunities than are being exploited to reduce the burden of heart disease. It is important that States have programs commensurate with the increasing knowledge and new concepts as they become available. The increase proposed would raise the base grant and would assure that the States with lower population and resources, although equal in disease burden, would be able to establish minimal programs and build a solid floor for further advances.

2. Direct operations, increase of $1,117,000

A. Research, increase of $115,000

The increase in this area would allow for major reorganization of two large laboratories in the intramural area. Each of these areas lost its laboratory chief during the past year. It is planned to expand and emphasize the cellular physiology and the biophysical aspects of cardiovascular research under a revised organizational structure and new direction.

B. Training, increase of $114,000

This amount would provide support for 11 additional trainees for specific roles in cardiovascular research. In the past year there were a greater number of technically qualified candidates than there were funds available, while the need for training of persons was not diminished.

C. Professional and technical assistance, increase of $600,000

The increase requested would be used for demonstrations of stroke restorative services and pilot studies in methods of stroke prevention.

Although it is known that more than 80 percent of the stroke victims who live can be restored to self-care and kept out of institutions, 30 States have no programs for restorative services. In addition, very little work has been done in prevention of strokes. It is proposed to implement the pilot study in prevention now under way in Oregon by one or more new studies in 1963, and to increase the restorative services demonstrations. In all about 18 projects can be supported.

D. Review and approval, increase of $242,000

Provision is made for additional staff to facilitate the review and approval of the expanded research grants program.

E. Administration, increase of $46,000

This increase would provide for strengthening of the immediate staff of the Office of the Institute Director as new areas of activity are constantly being developed and additional direction is required.

DENTAL

Comparison of 1963 President's budget with 1963 professional judgment budget estimate

[In thousands]

	1963 President's budget	Professional judgment budget estimate	Increase
Grants and related contracts:			
Research	$9,123	$9,695	+$572
Fellowships	882	1,230	+348
Training	3,741	5,500	+1,759
Total grants and related contracts	13,746	16,425	+2,679
Direct operations:			
Research	2,858	3,217	+359
Review and approval	424	450	+26
Administration	171	216	+45
Total direct operations	3,453	3,883	+430
Total estimate	17,199	20,308	+3,109

1. Grants and related contracts, increase of $2,679,000

A. Research, increase of $572,000

The increase requested would provide additional support in three project fields. (New grants and supplemental requests.)

1. Growth and development and congenital anomalies research	$242,000
2. Periodontal disease research	230,000
3. Behavioral science research	100,000
Total	572,000

B. Fellowships, increase of $348,000

The increase would provide support for 39 additional fellows in the predoctoral, postdoctoral, and special programs.

C. Training, increase of $1,759,000

Of this increase, $700,000 would be devoted to the chairside assistants program, allowing additional grants to new schools, and increasing the level of support in existing grantee institutions whose needs are greater due to increased enrollment.

The remaining $1,059,000 of this estimated increase would be used in two areas. The support level in 18 dental school institutions would be raised by $40,000, bringing their level of support to approximately $80,000 each. The approximate cost of this would be $700,000. New programs would be initiated in eight nondental school institutions (clinics, hospitals, universities) at the $45,000 level. The cost of this would be $359,000.

2. Direct operations, increase of $430,000

A. Research, increase of $359,000

Of the increase requested, $20,000 would be allocated to the biometric and epidemiological program for increased statistical processing needs connected with the expanding biological research activties in genetics and other areas; $82,000 would be for the support of five positions and related other object costs in connection with oral pharyngeal and genetic research programs in the clinical investigations branch; $65,000 would support five additional positions in experimental pathology; and the remaining $192,000 would be an increase to the NIH management fund for centrally furnished services.

B. Review and approval of grants, increase of $26,000

This increase would support three new positions and additional other object costs necessary to meet increased demands of the expanded grants program.

C. Administration, increase of $45,000

This increase would be for the support of one additional position over the 1963 President's budget, plus the support of early recruitment of the program analysis positions requested in the 1963 President's budget. Funds requested in that budget will not permit recruitment before one-half of the fiscal year has elapsed. A portion of the increase would be for reimbursement to the NIH management fund for centrally furnished services.

Comparison of 1963 President's budget with 1963 professional judgment budget estimate

[In thousands]

	1963 President's budget	Professional judgment budget estimate	Increase
Grants and related contracts:			
Research	$68,754	$80,000	$11,246
Fellowships	1,177	3,500	2,323
Training	9,525	11,000	1,475
Total grants and related contracts	79,456	94,500	15,044
Direct operations:			
Research	10,173	10,173	
Collaborative studies	650	1,000	350
Review and approval	1,337	1,590	253
Administration	305	305	
Total direct operations	12,465	13,068	603
Total estimate	91,921	107,568	15,647

1. RESEARCH AND RELATED ACTIVITIES, INCREASE OF $15,044,000

A. Research grants, increase of $11,246,000

1. Regular program, increase of $9,246,000.
2. Categorical clinical research centers, increase of $2 million.

B. Fellowships, increase of $2,323,000
C. Training, increase of $1,475,000

2. DIRECT OPERATIONS, INCREASE OF $603,000

A. Collaborative studies, increase of $350,000
B. Review and approval, increase of $253,000

Research projects, net increase $11,246,000

This activity contains the majority of Institute funds. Increases provided for NIAMD research projects during the past several years have been significant for several reasons. One is the awakened interest, on the part of research investigators, in categorical areas such as gastroenterology and diseases such as cystic fibrosis that until recently have been relatively neglected. This interest has been generated, in large measure, by vigorous Institute leadership, and encouraged and supported by Congress. Another reason is the assignment of responsibility for several additional research and training categories such as dermatology and orthopedics.

Further, the Institute's training and fellowship activities are relatively new. Their purpose, that of providing needed investigators, is only now beginning to be realized to any great extent. The researchers trained in these programs turn to this activity for the support to carry out the studies for which they have been preparing.

In all of the areas of responsibility of this Institute, a great deal of emphasis is placed on basic nonclinical research, the result of which lay the necessary foundation for clinical advances. These activities continue to expand rapidly and fruitfully with resultant benefit to all categorical disease areas.

Viewed, then, with the foregoing factors in mind, the present posture of the research projects program is considered to be normal, reflecting the healthy development of a large segment of biomedical research which has been provided the required stimuli.

It is now estimated that there will be about $4.7 million of approved, unpaid projects at the end of this fiscal year. The requested increase provides for payment of this backlog, and anticipates a continued increase in meritorious applications at about the same rate as in the past, requiring a further $4.5 million.

A small number of highly specialized clinical units as facilities for the performance of superior clinical research in metabolism and the rheumatic diseases are now being supported by this Institute. Preliminary reports indicate that these units are fulfilling a need not met by other clinical resource programs, and it is felt that reasonable expansion of the program is highly desirable. The requested increase provides $2 million for establishment and support of additional centers.

Fellowships net increase $2,323,000

This program complements the Institutes training grants program and provides research training in specialized environments where training grant support is not feasible. It also serves to implement training of investigators in areas in which sufficient training centers have not been established, such as dermatology and orthopedics.

Recent increases to this program have been specified for use for the research career awards program. This program is now underway, and full use will be made of available funds. However, these earmarked increases have precluded expansion of support for the postdoctoral, special, and other types in which increasingly significant backlogs have existed for several years and will recur again this year.

It is considered essential that additional funds be made available for this program if sufficient, properly oriented investigators are to be provided for disease categories currently receiving minimal attention, and to meet the ever-increasing total demand for well-trained personnel.

Training, net increase $1,475,000

The graduate training grant program emphasized the postdoctoral training of young physicians for careers in academic medicine with an emphasis on research in special fields of interest to this Institute. This is of prime importance in the provision of sufficiently trained investigators. Sums expended during the past several years have materially improved the existing supply of highly skilled manpower. However, the Nation's efforts in medical science are continually being expanded, creating a continuing need for more research personnel. The shortage of academic personnel for clinical research is of particular interest, as this Institute's primary training responsibility is in clinical investigation.

A new program with tremendous significance for the whole of medical research and research training characterizes the experimental clinical training program. The rapid buildup of our medical knowledge coupled with its everchanging nature has resulted in a constantly lengthening period of both pre- and postdoctoral training for the medical scientist. With the constantly increasing opportunities in and necessity for sound and large-scale clinical investigative activities, this problem becomes of major importance for the clinical investigator. Because he must acquire the skills of both the competent physician and the astute scientist, the tremendous burden of preparation is placed on the institution as well as on the individual. It seems highly improbable that the intensified demands of quality and quantity can be met by mere expansion of existing methods and approaches in this age of sharp competition for men, money, and minutes. Present patterns of training long antedate the tremendous expansion of our national medical research effort and reappraisals of current philosophies and practices are long overdue.

In order to provide the essential moral and financial impetus and support for study and experimentation to this end, therefore, a sum of $1 million is strongly recommended to fund this activity. Support of this magnitude would permit a few carefully selected schools to thoroughly develop totally new concepts to the whole problem of adequate training of medical investigators. The immediate investment of this relatively small sum would undoubtedly result, in future years, in a major conservation of personnel, facilities, and funds; denial or procrastination cannot be other than more costly than the Nation can afford as well as risking failure to provide the individuals in training with the most effective background with which to pursue their tasks.

The remaining $475,000 of the requested increase will be used to strengthen established training centers and, where possible, to establish new centers for recently assigned interests such as dermatology.

Collaborative studies, net increases $350,000

The requested increase is considered necessary for the continued development of the Institute's program in international nutrition research at the rate considered most desirable by the Institute and the advisory opinions of the Interdepartmental Committee on Nutrition for National Defense. The ability to make effective use of available funds has been demonstrated by developments to date, and a number of studies in selected countries throughout the world are planned. These will be both initial surveys and the followup variety required for the evaluation of past survey recommendations and determinations. The funds will be used primarily for research projects and attendant supporting expenses including travel, consultant salaries, and contracts and agreements with private organizations and other Government agencies.

Review and approval of grants, net increase $253,000.

The requested increase would provide required professional and clerical personnel to administer the expanded grants programs. This includes funds for personnel compensation, initial equipment, travel, printing, communications, and other miscellaneous expenses. It also provides for required services furnished centrally.

ALLERGY AND INFECTIOUS DISEASES

Comparison of 1963 President's budget with 1963 professional judgment budget estimate

[In thousands]

	1963 President's budget	Professional judgment budget estimate	Increase
Grants and related contracts:			
Research	$37,145	$46,597	$9,452
Fellowships	1,610	3,981	2,371
Training	5,350	9,750	4,400
Total, grants and related contracts	44,105	60,328	16,223
Direct operations:			
Research	10,005	10,205	200
Collaborative studies	4,050	[1] 4,050	[1] 0
Review and approval of grants	894	902	8
Administration	288	315	27
Total, direct operations	15,237	[1] 15,472	[1] 235
Total estimate	59,342	75,800	16,458

[1] Excludes a possible transfer of $1,150,000 from "Research grants" to "Collaborative studies" to bring the vaccine development program to the $2,000,000 level. The funds would be used to finance additional contracts as needed.

1. *Research and related activities, increase of $16,223,000*

A. Research grants, increase of $9,452

1. Regular program, increase of $8,952,000.
2. Categorical clinical research centers, increase of $500,000.

Virus infections.—The implementation of the viral reference reagents program as a collaborative study will provide valuable tools for research on these diseases. Availability of diagnostic reagents will permit more extensive research to establish the relationship between many of these infectious agents and human disease. It is anticipated that investigators who have not previously been engaged in this area of activity, particularly at the applied level, because of lack of availability of standardized and certified diagnostic materials will now be in a position to mount meaningful programs. The availability of reference reagents for identification of many viruses will also provide an opportunity for investigators to engage in much broader programs of a basic nature, including studies on many facets of the nature of these infectious organisms. In addition to the many projects which the viral reference reagents program will make possible, this program will require a constant flow of basic information in order to identify areas of priority interest and to serve as a foundation for its more applied activities.

The vaccine development program, which is also being conducted as a collaborative study, is bridging the gap between fundamental research and the development and production of vaccines. As this work progresses, a constant supply of information stemming from fundamental research will be required to make the program meaningful.

Tropical medicine.—Several of the parasitic and other infectious diseases which are most often found outside the United States are of immediate practical importance either because of the threat of introduction into this country, because of their importance to our citizens who find themselves in areas where these diseases are endemic, or because of their potential impact on the total economy of countries with which other agencies of the Government have cooperative programs. An excellent example of the latter is the disease schistosomiasis, the control of which is vital to irrigation projects and other changes in natural environment of many countries. Basic research can provide a foundation on which the development of an immunizing agent against this disease might prove feasible. Recent upsurges of cholera and cholera-like infections in other countries are another example of the constant threat posed by diseases which are not normally found within the United States and on which more research, both basic and applied, is needed.

Staphylococcal and related infections.—The constantly changing pattern of infections caused by staphylococcus and other organisms, particularly in hospitals, has been shown to result from a multiplicity of factors varying tremendously from institution to institution. Further knowledge of these factors and the role they play in the pattern of infections is essential to a rational solution of these problems. Extensive research on the basic nature and life processes of these infectious organisms can be expected to yield information needed for the implementation of practical control measures and a better understanding of the resistance of organisms to antibiotics.

Virus chemotherapy.—To date, relatively little progress has been made in the control and treatment of virus infections by antibiotic agents. The phenomenal success of these agents in the treatment of a wide spectrum of bacterial disorders lends hope to eventual future success in efforts to develop chemotherapeutic agents of similar efficacy against viruses. The currently available basic information does not yet appear adequate as a foundation for the immediate development of such chemotherapeutic agents. Nevertheless, additional research on the nature of viruses, the infectious process and the relationships between viruses and cells of the host, conducted in an expectant research atmosphere, could lead to progress in virus chemotherapy.

Normal program expansion.—In spite of budgetary increases in 1962, it appears that there will be a substantial number of new research grant applications remaining unpaid through lack of funds at the beginning of 1963. This is true even though those applications favorably recommended by the National Advisory Allergy and Infectious Diseases Council but with relatively poor ratings have been removed from the list of applications eligible for payment. Projections based on past experience indicate that substantial increase in normal program funds will be required if this Institute is to award the anticipated new applications recommended for approval, meet our obligations for continued support of ongoing projects, increase the categorical clinical center program, invest a proportionate share of our funds in the general research support grants, and increase Public Health Service participation in indirect costs.

B. Fellowships, increase of $2,371,000

It is estimated that after all funds available in 1962 are used for the payment of fellowships and awards, there will remain applications approved but unpaid through lack of funds in the amount of $300,000. Initiation during 1962 of the research career award program means that a substantial portion of our funds will be needed to honor the long-term moral commitments accompanying these awards. The fellowship and award program has continued to be most popular and beneficial since it provides an opportunity for the individual scientist to receive the guidance and experience necessary for him to develop his own potential in an environment and under the guidance of a mentor of his choice, and in the special scientific field of greatest interest to him. It is estimated that an additional $2,371,000 would be required to support the number of worthy individuals requesting support for the first time, to pay those fellowships already recommended for approval but unpaid through lack of funds, and to provide support for new research career awards approximately equal in number to those awarded during 1962.

C. Training, increase of $4,400,000

The graduate training grants program is currently carrying commitments for support from 1963 funds of approximately $3,384,000. Estimated Council recommendations to continue current training programs which do not presently have commitments for 1963 will require $883,000. Projected supplements to existing programs amount to $1,083,000. Thus, $5,250,000 will be required to continue existing training activities at an appropriate level.

Overall program objectives and appropriate activities to obtain such objectives are at this moment undergoing a thorough review and analysis. Until this analysis is complete, it is difficult to outline specific program areas to be stimulated. It does appear, however, that approximately $4,400,000 would be required to fully implement a graduate research training grant program of appropriate magnitude and that there are sufficient opportunities for the establishment of good training programs to justify an investment of this magnitude.

2. Direct operations, increase of $235,000

A. Research, increase of $200,000 and 15 positions

Virus identification and serology laboratory.—Eight positions and $95,000 are requested to complete the staffing and facilities of this unit. Approximately $45,000 will be used for salaries and related costs, and $50,000 for the purchase of reagents necessary for the identification of the many strains of virus. This unit supports clinical and ecologic studies in relation to virus as a cause of cancer and the investigations on the role of viruses in acute respiratory diseases. The scores of viruses possibly incriminated in tumor growth and definitely so in various types of respiratory diseases including the common cold, necessitate a comprehensive and complete approach to their identification. Antigen and specific antisera of high quality are required. These can be purchased on specific order from various commercial establishments. The additional positions will provide technicians to conduct these procedures.

Field station in Hawaii.—Four positions and $65,000 in additional funds are necessary to provide the full facilities for this unit. A newly recognized disease, eosinophilic meningitis, is known to occur in Hawaii and has been reported in epidemic form in several islands of the Pacific area. It is now believed to be caused by a parasite with a reservoir in nature. The unit in Hawaii will provide the laboratory and field base for a comprehensive investigation of this potentially important disease. The unit which is intended to be a temporary field party, established for a period of 3 to 5 years, will also be available for investigation of virus diseases of specific importance to Hawaii and to the other islands of the Pacific. Arrangements can be made with the Queens Hospital, Honolulu, to provide excellent laboratory space and animal facilites and the necessary technical services.

Malaya field installation.—Three positions and $30,000 are requested for additional support for this unit located in Kuala Lumpur, Malaya. Since the summer of 1960, Institute scientists have been working in a temporary field station in connection with the Medical Research Institute, Malaya, and the U.S. Army research unit there on problems of malaria infection in monkeys and its relation to human malaria. The possibility that monkeys may serve as a reservoir for human malaria is being investigated in various parts of Malaya, as strains of malaria parasites recovered in this country have been shown to infect man experimentally. This question is now one of the more important to be solved in the problem of malaria, a disease which remains one of the major public health problems of the world.

Management fund.—The increase of $10,000 would provide additional support for the services furnished centrally by the National Institutes of Health management fund.

B. Collaborative studies, no increase.

NOTE.—No increase is shown under this activity, but a possible transfer of $1,150,000 from research grants to collaborative studies is being considered. This increase would bring the vaccine development program up to the $2 million level. The funds would be used to finance additional contracts with various institutions.

C. Review and approval of grants, increase of $8,000

The increase of $8,000 would provide additional support for the services furnished centrally by the National Institutes of Health management fund.

D. Administration, increase of $27,000

If additional funds were made available, they would be used to support existing positions requested in the 1963 President's budget. These funds would provide the amount required to support the positions for at least 75 percent of the year. It has been found that the seven new positions requested in the President's budget will require considerably more than the related $20,000 presently provided. The funds will also provide necessary related equipment and supplies.

NEUROLOGY AND BLINDNESS

Comparison of 1963 President's budget with 1963 professional judgment budget estimate

[In thousands]

	1963 President's budget	Professional judgment budget estimate	Increase
Grants and related contracts:			
Research	$46, 421	$59, 216	+$12, 795
Fellowships	1, 723	2, 000	+277
Training	8, 765	15, 700	+6, 935
Total grants and related contracts	56, 909	76, 916	+20, 007
Direct operations:			
Research	6, 566	6, 566	0
Collaborative studies	3, 496	3, 496	0
(Construction, Puerto Rico) [1]	[1] (600)	(800)	(+200)
Training activities	50	50	0
Professional and technical assistance	2, 300	3, 000	+700
Review and approval of grants	1, 499	1, 499	0
Administration	386	386	0
Total direct operations	14, 297	14, 997	+700
Total estimate	71, 206	91, 913	+20, 707

[1] Included officially in the appropriation "Buildings and facilities," PHS.

1. Grants and related contracts, increase of $20,007,000

A. Research grants, increase of $12,795,000

1. Regular program, increase of $11,285,000.
2. General research support grants, increase of $1 million.
3. Scientific evaluation and planning, increase of $10,000.
4. Categorical clinical research centers, increase of $500,000.

For 1963, it is estimated that the continuation requirements and the normal growth of new approved applications will be approximately $48 million, and a total of approximately 1,828 projects.

Estimated approved grants	$48,066,000
Following are special program areas of particular concern:	
Clinical research center and program project grants: Increasingly, neurological research is coming to depend upon long-term projects requiring the use of complex equipment and involving a variety of technical skills. Such projects can evolve only upon a base of broad continuing support. As a participant in the new NIH programs of clinical center grants and research program-project grants the Institute is offering support to medical institutions (1) engaged in a multidisciplinary attack on specific diseases of importance in the neurological and sensory field or (2) engaged in a disciplinary attack on a group of neurological and sensory disorders. In addition to the support of research, these programs provide for the establishment of research, patient beds, clinical supporting laboratories and for the salaries of key staff. Funds will be available for the operational support of research resources through either a clinical research center grant or as part of a research program-project grant.	
Under this particular program, we will be particularly interested in the development of research efforts in such specific problem areas as epilepsy, cerebral palsy, multiple sclerosis, cerebrovascular diseases, disorders of vision and hearing, and neurological diseases of infancy. Currently we are supporting 11 such projects	3,500,000
The development of a broad program for the development and evaluation of drug and other therapies, including those for epilepsy, Parkinsonism, myasthenia gravis, cerebral palsy, and disorders of vision, including uveitis and glaucoma	1,000,000
Projects with industry for the development of special instruments, and for the adaptation of industrial techniques to special problems in medical research. This will include such things as certain new computer techniques applicable to the the study of neuropathological material, electronic devices for the study of nervous activity, and special devices for the testing of intraocular pressure for the removal of foreign bodies from the eye	1,000,000
International cooperative research programs, including the special areas of cerebrovascular disease and perinatal studies	500,000
General research support grants	4,300,000
Scientific evaluation and planning	50,000
Additional indirect costs	800,000
Total, research grants	59,216,000

B. Fellowships, increase of $277,000

Applications for fellowships have increased in the fields of neurological and sensory disorders. This increase will support a total program of 173 awards for $2 million, as compared to 151 awards and $1,723,000 in 1962.

	1962		1963	
	Number	Amount	Number	Amount
Postdoctoral	89	$623,000	100	$700,000
Research career awards	62	1,100,000	73	1,300,000
Total	151	1,723,000	173	2,000,000

C. Training, increase of $6,935,000

Graduate training grants.—The basic thesis underlying the development and support of the training programs is that research in the neurological and sensory disorders requires an expanded supply of adequately trained preclinical and clinical research personnel. The study of the nervous system is a complicated and difficult field. Research in this field requires long periods of specialized training. Only recently have adequate tools and methods for investigation become available. As new research techniques evolve, training in these improved techniques is essential. A large proportion of the men doing research in this field are therefore young investigators trained in research training programs stimulated or supported by this Institute.

The ultimate objective of the Institute is to see established within every medical school a focus for research in neurology, in ophthalmology, and in otology, as well as highly specialized regional research and research training centers in these disciplines. At the present time only a small number of medical schools have a single full-time faculty man in each of these specialties. If we are to have clinical investigators to staff these positions, we must provide research training opportunities for those preparing for careers in these areas.

Our most recent studies of the status of the basic neurological sciences are most revealing. Neurophysiology, although inadequately staffed, is probably better staffed than are other neurological research disciplines. There is an acute shortage of research personnel in neuropathology. Twenty to thirty medical schools have no one on their staffs in this important research area. At the present time, there are fewer than 30 men in training in this area. For neurochemistry—probably one of the most hopeful new approaches to the study of neurological disease—there are less than 10 research training centers in the country. There are only 18 men in training for this research specialty. In the entire neurological and sensory preclinical sciences training program—neuroanatomy, neuropathology, neurophysiology, neurochemistry, and neuropharmacology—we support approximately 120 special research fellows. Under these circumstances of desperate need, a primary objective of this Institute's research training grant program is to increase the number of research training programs and research trainees in the above fields. Our estimates of immediate program needs are based on our estimate of the manpower available to mount these programs.

Undergraduate training grants.—Undergraduate training grants would be awarded on a competitive basis to selected schools of medicine, osteopathy, and public health to stimulate the development of improved training programs related to the cause, diagnosis, and treatment of neurological and sensory disorders. These grants will serve to stimulate neurological and sensory disease research interests by giving students a chance to become better acquainted with the problems in these areas and participate in the research activities of these departments in the medical schools. Because of this stimulus, additional medical students would be attracted to research and teaching careers in the neurological and sensory disease sciences. The undergraduate training grant program will thus complement the graduate training grant program and serve to stimulate the development of training programs in those institutions not yet able to participate in the Institute's graduate training grant program.

1963 projection:	
Continuation of 1962 program:	
Continuations	$5,200,000
Competing continuations	1,500,000
Supplementals	456,000
Stipend increases	275,000
Approved but unpaid in 1962 (27)	1,700,000
Total	9,131,000
Support of 50 new graduate training programs	2,000,000
Support of 100 undergraduate training grants	2,500,000
Traineeships	2,069,000
Total, training	15,700,000

2. Direct operations, increase of $700,000

A. No increase for the activities other than professional and technical assistance is proposed

However, reference is made to the "Buildings and facilities," PHS appropriation for construction proposed in Puerto Rico for the laboratory of perinatal physiology.

It is proposed that $800,000 is necessary to build a suitable research facility on the grounds of the medical center of Puerto Rico. In this facility, we would hope to consolidate all of the present research going on in space at the PHS outpatient clinic, the University of Puerto Rico's Medical School, and at Bethesda. Current laboratory operations occupy approximately 12,000 square feet.

B. Professional and technical assistance, increase of $700,000

This amount is requested to expand and further develop the new program initiated during fiscal year 1962 for the purpose of applying research findings in the neurological and sensory disease areas to the prevention, diagnosis, treatment, and rehabilitation of persons suffering from these disorders. This strategic new program is developing along several major lines and these funds will be used to further implement these developments.

In fiscal years 1962, negotiations are being conducted with several institutions for the development of special community neurologic and sensory disease projects. Also, a training grants program will be initiated in 1962 to provide assistance to institutions for training badly needed professionals in neurology, otolaryngology, and ophthalmology. Developmental work is being done for the initiation of a neurologic and sensory disease information clearinghouse for the collection and dissemination of information, and the groundwork has been laid for the beginning of a project grants program to provide service in neurologic and sensory diseases at the community level.

There is a great need for improved information and communication in the neurological and sensory disease areas. It is proposed to expand the distribution of general information, as well as technical information, in the fields of neurological disease, speech and hearing disorders, and visual impairments. This will include improved techniques to provide the latest scientific information to practitioners providing direct service at the community level. These activities will be undertaken through direct operation of the program on a national basis as well as sponsorship or support of seminars, consultation, and other scientific and educational activities at the community, State, and regional level. Preparation of films, filmstrips, other visual aids, periodicals, and other publications will be utilized in this expanding important communication effort. Procedures are now being developed for rapid communication with practitioners, and an early beginning will be made in the publication of scientific digests and information newsletters.

A great need exists across the country for adequate community services for neurological and sensory patients. Improvement and expansion of individual and community services will be fostered through the support of project grants, demonstrations, and technical services. Pilot projects will serve as basis for action to stimulate the improvement of existing community services and their extension, both in terms of the population served and the types of disorder treated. In cooperation with other agencies or institutions, or through grants, demonstrations, and seminars at the community, State, and regional level, the utilization of current scientific developments in a comprehensive approach to community services for neurological and sensory patients will be stimulated to replace the traditional segmented services which are wasteful of skilled manpower, limited to small groups of persons, and expensive.

Another example of such an activity is the development of a national screening field trial for phenylketonuria. New techniques appear to provide the ability to diagnose this disease within the first week of life.

Effective high-quality services depend on the working together of a number of special disciplines and skills in proper order and timing, and adequate manpower is lacking to provide these needed services. Additional needed medical and other health personnel will be produced through the expansion of the training grant program previously developed. Improvement in the quality of service currently available will be provided by expanding and extending pilot projects now under development to provide community institutes and seminars in current scientific developments and techniques.

Special projects will be initiated in which the interests and skills of the various institutions in a community with special competence in the neurological and sensory disease field can be brought together and stimulated. Through the establishment of strong, cooperative interrelationships between these institutions and surrounding communities, effective foci will be developed both as facilities for the training of service personnel and as community service laboratories to produce new techniques in patient referral and followup, improved methods of diagnosis and treatment, including restorative services following acute disease manifestations, and technical consultation to communities where limited numbers of skilled personnel are available.

Opportunities and methods for putting available knowledge into practice must be identified and tested in practical applications. Some of these funds will be used to obtain this vitally needed information on morbidity and distribution in the population, manpower, and services requirements, and for evaluation of existing programs. This will be carried out through surveys, field investigations, epidemiologic studies, and other techniques through direct services available to the program and through contracts and grants to other agencies and groups, who are able to make this kind of assessment, such as the National Health Survey, Bureau of the Census, State health departments, professional organizations, and so forth. Such a comprehensive undertaking in the fields of neurological and sensory disorders has not been adequately carried out before. Some of these studies will be of short-term nature in order to provide immediate information for program development and pilot projects. Other studies and activities will be, of necessity, longer range projection in order to provide continued and more accurate data for the Nation as a whole.

CHILD HEALTH RESEARCH CENTER

Mr. Fogarty. I notice a recent press release regarding the appointment of a Director of the Center for Research on Child Health. Is there any change in the function of this center since we discussed it last year?

Dr. Shannon. No, sir.

Mr. Fogarty. It operates about the same as the Center for Aging which was established a couple of years ago; doesn't it?

Dr. Shannon. Precisely so, yes, sir.

Mr. Fogarty. The Center for Aging hasn't come up with much.

Dr. Shannon. Neither the Center for Aging, nor this new one on child development, has what I should call program responsibilities. It is primarily a staff office for the various Institutes, and it serves as a source of information for those in academic world who wish to learn precisely what the opportunities are for support in its general area of cognizance.

It has no operating budget. It has no operating responsibilities, save those that relate to our staff operations.

Mr. Fogarty. Is it costing the Government any money?

Dr. SHANNON. Oh, yes. We depend on what it does. It brings several functions together at one point; but these functions would have to be discharged somewhere. In general it saves the Government money because it serves as a single point source where authoritative information can be made available, so that an institution interested in developing a program in aging research—or in child health—will not have to correspond with several Institutes in order to determine what are the opportunities in our programs.

So I think, beyond doubt, it saves the Govenment money and provides better public service.

DESCRIPTION AND FINANCING OF EACH RESEARCH GRANT PROGRAM

Mr. FOGARTY. We would like to get in one place in the record a detailed explanation of each research grant program, the total budget of each and what was spent for each of the last 4 years, and what in your professional judgment we ought to do in the future.

Dr. SHANNON. Yes, sir. We shall be glad to submit that.

(The requested information follows:)

REGULAR RESEARCH GRANTS

1. *Purpose of program.*—To provide grant support of research in health, medicine, and allied fields with the major objectives (1) of expanding medical and biological research activities in universities, hospitals, laboratories, and other public or private institutions, and (2) of stimulating new investigations in fields needing exploration. The grant ranges from support of smaller, discrete, and circumscribed projects, which are defined as project grants, to support of broad programs which integrate the research interests of several investigators, and which are called program project grants.

2. *Funds.*—

1959 obligations	$139, 629, 000
1960 obligations	185, 474, 000
1961 obligations	240, 607, 000
1962 estimate	308, 230, 000
1963 estimate	377, 064, 000

3. *Present stage of development.*—The modest cancer grants program of 1938–45 of less than $100,000 annually changed in 1946 to a health, medicine, and related sciences program of $780,000. Steady annual increases since 1946 have produced the 1962 program of almost $400 million. This $400 million will support more than 15,000 research projects conducted in almost 1,500 institutions throughout this country and abroad, and covering the full range of biological and related research. While the program continues in major part to support the ideas of investigators in the grantee institutions, a significant part of the grants provide support of programs reflecting initiative of NIH staff, such as cancer chemotherapy, psychopharmacology, and other collaborative programs.

4. *Plans for the future.*—The NIH believes that medical research should continue to expand as long as this country is faced with major crippling and killing diseases and conditions. Further, it believes that a number of factors contribute together to provide full assurance that substantial expansion can be effected. These factors include (1) a sharp expansion in the population base from which new M.D.'s and Ph. D.'s will be drawn, (2) a steadily rising college enrollment, (3) a significant percentage increase in graduate enrollment, and (4) improving educational opportunities for the more talented students, including both new medical schools and strengthened graduate and professional schools.

GENERAL RESEARCH SUPPORT GRANTS

1. *Purpose of program.*—To provide funds for the general support of the medical research and research training programs of institutions under conditions enabling the recipients to meet needs which are not being effectively met by existing forms of support.

2. *Funds.*—The amount available for distribution for this program will constitute "such uniform percentage, not to exceed 15 per centum as the Surgeon General may determine, of the amounts provided for grants for research projects for any fiscal year through the appropriations for the National Institutes of Health * * *" (Public Law 86–798). In 1962, approximately 6 percent of the total appropriation for regular research projects will be devoted to general research support grants.

1962 estimate	$20,000,000
1963 estimate	30,000,000

3. *Present state of development.*—General research support grants, totaling $20 million, have been approved for 153 schools of dentistry, medicine, osteopathy, and public health. The formula for distribution of the grant provides funds proportionate to the volume of research conducted by these institutions.

4. *Plans for the future.*—Eligibility to receive general research support grants will be extended in fiscal year 1963 to those schools of nursing, schools of veterinary medicine, hospitals, and other nonprofit research organizations that are determined to be heavily engaged in research related to health.

Each institution receiving a general research support grant will submit an annual report describing the utility of the grant in strengthening specific activities in health research and research training. The report will also contain a carefully considered assessment of the institutional functions aided by the grant funds.

CLINICAL RESEARCH CENTERS[1]

1. *Purpose of program.*—To provide grants to non-Federal research institutions for establishment of biomedical research centers of resources. These centers make possible the performance of meritorious and complex clinical investigation in the preclinical, clinical, and health-related sciences. They provide the opportunity for precise observations and controls which are essential to studies with patients. These centers administratively may be viewed as (*a*) categorical and (*b*) general. The categorical centers are supported by the appropriate Institute and are concerned primarily with a specific category or type of disease, such as heart disease or cancer, toward which the work of the particular Institute is oriented. In the general clinical research centers, which are supported by the Division of General Medical Sciences, the research activity is not focused primarily on a single Institute-related category of disease, but rather on categories of disease and on numerous areas of preclinical and clinical science. All centers consist of discrete facilities with specialized bed arrangements, core laboratories, and trained personnel. They use a multidisciplinary approach wherein investigators with varied interests and techniques share the center's facilities. The centers are highly conducive to the advancement of knowledge regarding human health and disease.

2. *Funding.*—See attached worksheet.

3. *Present state of development.*—The earlier of the centers programs, general clinical research centers, is now well underway with 40 grants having been made to 38 institutions as of January 1, 1962. By the end of fiscal year 1962, some 60 centers are anticipated. Since the initiation of the program 2 years ago, approximately half the centers have begun to admit patients. Important scientific accomplishments have already been noted.

Approximately 60 grants for categorical clinical research centers and facility portions of program projects have been awarded. Almost half of these are supported by the NIH. As with the general clinical research center program, the categorical programs have made important progress.

4. *Plans for the future.*—With the accumulated experience gained from the various center operations, NIH is now able to focus its attention on the achievement of a more coordinated characterization of what constitutes effective center operations.

Both the categorical and general clinical research centers programs as well as the physical resources portions of program projects are expected to increase in scope of activity in order to fulfill anticipated needs.

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[1] Includes physical resources portions of program projects.

Funding of clinical research centers program (research center grants and physical resource component of program project grants)

[In thousands]

	Obligations, 1960	Obligations, 1961	Estimate, 1962	Estimate, 1963
DGMS	[1] $2,993	[1] $8,000	$27,000	$33,500
Cancer	-------	4,199	7,500	7,500
Mental	-------	509	1,000	1,000
Heart	-------	3,962	7,000	7,000
Dental	-------	-------	-------	-------
Arthritis	-------	-------	500	500
Allergy	-------	-------	500	500
Neurology	-------	537	1,000	1,000
Total	2,993	17,207	44,500	51,000

[1] Includes obligations incurred against funds appropriated to the categorical institutes totaling $3 million.

SPECIAL RESOURCE CENTERS

1. *Purpose of the program.*—To provide grants to non-Federal research institutions for support of specialized facilities for instrument and electronic development, computing and data processing, and other specialized services. This program will enable research institutions to apply the phenomenal achievements of the basic biophysical and bioengineering sciences to the quantitative resolution of major problems of biology and medicine.

2. *Funding.*—

1962 estimate	$5,000,000
1963 estimate	5,000,000

3. *Present state of development.*—During the first few months of this program's life diverse needs for grant support of special resource centers have appeared. Depending on the orientation of the applicant, these needs have ranged from semiroutine intrument fabrication to advanced and highly sophisticated conceptual programs of great promise. The advice of experts in the computer and bioengineering fields is being sought and panels of consultants are guiding the development of these center programs. It is probable that the special resource centers will be most effective when coupled to a significant allied research program of such challenge as to attract and hold research men of brilliance. The greatest program needs thus far identified by NIH advisers are in this field of coupling biological phenomena, which are not presently measurable with accuracy, to electronic and similar instrumentation.

4. *Plans for the future.*—Until there is an opportunity to evaluate ongoing programs, the support for special resource centers will remain at the $5 million level.

PRIMATE RESEARCH CENTERS PROGRAM

1. *Purpose of program.*—To provide funds for the construction and basic operation of special research facilities or centers devoted to the advancement of all areas of knowledge on the biological characteristics of species structurally and physiologically similar to man throughout the entire life span of the subhuman primate. The objective is to acquire basic scientific information which will ultimately be useful in the prevention and treatment of human disease. Research facilities provided by this program are available to visiting scientists from all areas of this country and abroad.

2. *Funds.*—

1960 obligations	$1,917,275
1961 obligations	7,000,000
1962 estimate	7,000,000
1963 estimate	4,000,000

3. *Present stage of development.*—The construction of the first regional primate research center initiated in 1960 through grants awarded to the Medical Research Foundation of Oregon at Portland, is now nearing completion. Grants for the construction and operation of centers at the University of Wisconsin at Madison and the University of Washington at Seattle were awarded in 1961, and both of these centers are in the construction planning phase. A fourth application, from

Emory University in Atlanta, Ga., was approved for award from 1961 funds, subject to certain negotiations as directed by the National Advisory Heart Council. It is anticipated that the funds for new construction in 1962 will be utilized in following the council's recommendation that two additional regional centers be established; one in New Orleans, La., and one in Boston, Mass. Also, it has been recommended that a primate conditioning center be established to study procurement and maintenance methods and to evaluate a wide range of subhuman primates in terms of their specific usefulness in medical research.

4. *Plans for the future.*—In the primate center program, during 1963, the requested funds will allow for the support, maintenance, and some supplementation of the regional research centers already established or proposed for initiation in 1962.

INTERNATIONAL CENTERS FOR MEDICAL RESEARCH AND TRAINING

1. *Purpose of program.*—Grants are made to American universities to establish centers within their own organizations and affiliate centers within foreign institutions to broaden collaborative research and research training within the biomedical fields.

2. *Funds.*—In 1961, the initial year of the program, six of the Institutes (except the Dental Institute) and the Division of General Medical Sciences contributed to the support of the program which was administered by the National Institute of Allergy and Infectious Diseases. In 1962 the program will continue under the same administrative mechanism, except that the Heart and Arthritis Institutes' support was absorbed by the Allergy Institute. In 1963 the administration of the program will be handled by the Office of International Research, part of the Office of the Director, NIH, and will be funded in its entirety through the "General research and services, NIH" appropriation.

1961 obligations	$1,937,000
1962 estimate	3,192,000
1963 estimate	3,192,000

3. *Present stage of development.*—There are five centers currently being supported, and it is planned to initiate another in the latter part of 1962. The institutions involved and their respective programs are as follows:

A. University of California Schools of Medicine and Public Health, and the Hooper Foundation in collaboration with the Institute for Medical Research, Kuala Lumpur, Malaya.

The research program is initially centered on arthropodborne virus diseases, mycology, endocrinology, parasitology, and entomology with training emphasis in the fields of endocrinology-metabolism, biochemistry-immunology, microbiology-virology, geographic pathology, and medical ecology.

B. Johns Hopkins University School of Hygiene and Public Health and Department of Medicine in collaboration with the School of Tropical Medicine, Calcutta.

The research program has primary interests directed to the fields of pathobiology and general medicine, with emphasis on hematologic, infectious, neoplastic, and nutritional diseases.

C. University of Maryland School of Medicine in collaboration with the Institute of Hygiene, Lahore, West Pakistan, and other cooperating institutions in the area.

The general research program has emphasis centered initially on fevers of unknown origin, gastrointestinal infections, parasitology, pulmonary disorders, nutrition, pediatrics, preventive medicine, and epidemiology.

D. Tulane University School of Medicine in collaboration with the Universidad del Valle, Cali, Colombia.

The research program is directed primarily to studies on fevers of unknown origin, enterobacteria and shigella, tuberculosis in children, mycotic diseases, general virology, nutrition, cardiovascular diseases, hematology, cysticerosis, demography, sociology, and maternal and child health.

E. Louisana State University (New Orleans): The faculty of the school of medicine is pursuing studies in Central America.

The overall research approach will include studies in virology, bacteriology, parasitology, mycology, metabolism, biometry, and pathology of chronic diseases, such as cancer and vascular diseases.

4. *Plans for the future.*—No increase for this program is being requested beyond the 1962 level to allow more time for the evaluation of these administratively complex operations. Furthermore, additional time will permit the program administrators to accumulate more data to determine the optimum balance between the investment in these centralized oversea units on the one hand, and support of individual international projects on the other hand.

SCIENTIFIC EVALUATION AND PLANNING GRANTS (CHAIRMAN'S GRANTS)

1. *Purpose of the program.*—To provide funds for the assistance of the National Advisory Councils through the technical and scientific review of grant applications, and through the support of meetings used for the exchange of scientific views.

2. *Funds.*—

1961 obligations	$1,734,000
1962 estimate	1,885,000
1963 estimate	1,885,000

3. *Present stage of development.*—Research grant applications are reviewed prior to submission to the advisory councils by the appropriate study section. Each of these sections have scientific competency in a particular field or research discipline, and each is comprised of outstanding civilian authorities in the relevant specialties. In the training area, individual applications are reviewed by groups called committees. Both the study sections and the committees are supported by chairman's grants.

In addition to financing these review activities, chairman's grants support an extensive group of ad hoc panels, symposiums, conferences, and other types of meetings used for the exchange of professional views.

Scientific evaluation and planning grants (chairman's grants)—Source of funds

	Research	Fellowships	Training	Total
1961 actual:				
GRS–NIH	$728,000	$20,000	$295,000	$1,043,000
Cancer	289,000			289,000
Mental	72,000		35,000	107,000
Heart	15,000		10,000	25,000
Dental	12,000		8,000	20,000
Arthritis	15,000		55,000	70,000
Allergy			35,000	35,000
Neurology	35,000		110,000	145,000
Total	1,166,000	20,000	548,000	1,734,000
1962 estimate:				
GRS–NIH	848,000	20,000	295,000	1,163,000
Cancer	320,000			320,000
Mental	45,000		40,000	85,000
Heart	25,000		10,000	35,000
Dental	15,000		12,000	27,000
Arthritis	40,000		60,000	100,000
Allergy			50,000	50,000
Neurology	40,000		65,000	105,000
Total	1,333,000	20,000	532,000	1,885,000
1963 President's budget:				
GRS–NIH	848,000	20,000	295,000	1,163,000
Cancer	320,000			320,000
Mental	45,000		40,000	85,000
Heart	25,000		10,000	35,000
Dental	15,000		12,000	27,000
Arthritis	40,000		60,000	100,000
Allergy			50,000	50,000
Neurology	40,000		65,000	105,000
Total	1,333,000	20,000	532,000	1,885,000

REGULAR RESEARCH FELLOWSHIPS

1. *Purpose of program.*—The purpose of the program is to support the training of qualified scholars for research and academic careers in the basic and clinical sciences in health and health-related fields and thereby to increase the number of trained research investigators and teachers in these fields.

There are three major categories of regular research fellowships: predoctoral, postdoctoral, and special.

Predoctoral fellowships are to assist individuals who have a bachelor's degree or equivalent in such training in the aforementioned fields as leads to a master's or doctoral degree. Postdoctoral fellowships are to support additional training for an individual who already has an earned Ph. D., M.D., D.D.S., D.V.M., or equivalent degree. Special fellowships are to support groups of fellows who fit into one of the following: (1) those who have had at least 3 years of relevant research and/or professional experience after receipt of the doctoral degree; (2) those who have completed residency training requirements in a clinical specialty or its equivalent; and (3) those who need special training not met by other fellowship programs although they do not have a doctoral or equivalent degree.

2. *Funds.*—

Obligations	Regular research fellowships			
	Predoctoral	Postdoctoral	Special	Total
1959	$3,180,000	$3,728,000	$901,000	$7,809,000
1960	4,783,000	5,332,000	1,342,000	11,457,000
1961	5,200,000	6,857,000	2,188,000	14,245,000
1962 eatimate	3,753,000	7,709,000	2,035,000	13,497,000
1963 estimate	3,728,000	7,608,000	2,161,000	13,497,000

3. *Present stage of development.*—Approximately 995 predoctoral fellows will be supported in 1962 for the general, mental, and dental programs. Postsophomore and part-time support formerly included in this category will now be supported through general research support grants. This accounts for the decline of over 1,450 predoctorals from the 1961 level. Approximately 1,083 postdoctoral fellows will be supported in 1962 by all Institutes and the general program. This is a slight increase over the 1961 level. Approximately 220 special fellows will be supported in 1962 by all programs except neurology. This is a decline of 15 from the 1961 level.

4. *Plans for the future.*—There is no significant change in the regular research fellowship for 1963 from the 1962 estimate.

RESEARCH CAREER AWARDS

1. *Purpose of program.*—The purpose of this program is to provide increased numbers of stable career opportunities for scientists of superior potential and capability in the sciences related to health. The program includes young investigators who desire experience and further training in a productive research environment; scientists need experience to qualify for senior positions; and experienced investigators who are continuing to develop in productive careers of independent teaching and research.

2. *Funding.*—The career research award program was initiated in 1962 by merging and modifying the career research professorship part of the special fellowship grant, and senior fellowship grant programs. The latter program was in operation from 1959 to 1961; and the special fellowship grant program only in 1961. Although funds were available in 1961 for the career research professorship program, policy matters were not resolved in time to make awards. The funding follows:

	Obligations			1962 estimate	1963 estimate
	1959	1960	1961		
Senior fellowship	$2,000,000	$2,999,000	$4,474,000		
Special fellowship			424,000		
Research career awards				$11,799,000	$11,799,000
Total	2,000,000	2,999,000	4,898,000	11,799,000	11,799,000

3. *Present stage of development.*—Approximately 754 research career awards will be made in 1962 by all Institutes and the general program. This represents a 100-percent increase over the 1961 program level.

4. *Plans for the future.*—The 1963 President's budget maintains the program at the 1962 level.

FOREIGN FELLOWSHIPS

1. *Purpose of the program.*—The purpose of the program is (*a*) to provide free exchange of ideas and technical information between young, promising research workers of other countries and scientists of the United States; (*b*) to establish person-to-person relationships whereby continuing research arrangements between the laboratory to which the fellow returns and his host laboratory in the United States; and (*c*) to provide training in U.S. laboratories for young research scientists from other countries much as they provide training in their laboratories for U.S. scientists.

2. *Funds.*—

1959 obligations	$345,000
1960 obligations	400,000
1961 obligations	700,000
1962 estimate	700,000
1963 estimate	700,000

3. *Present stage of development.*—Selection of fellows is based on nomination by a committee of scientists in participating countries. The program was established in Western Europe in fiscal year 1958 with 12 countries participating. Plans were made at that time for an orderly increase in the number of participating countries based on research potential and likelihood that returning fellows could use training received in the United States. The increase in the number of participating countries has progressed according to schedule as follows, 1959, 30; 1960, 36; 1961, 40; and in 1962, 43. The number of fellows who will be supported in 1962 is 93, an increase of 1 over 1961.

4. *Plans for the future.*—The 1963 President's budget maintains this program at the 1962 level.

TRAINING GRANTS

1. *Purpose of program.*—To provide grant support of training in specified aspects of health, medicine, and allied fields with the major objectives of (*a*) insuring an adequate supply of competent research manpower, (*b*) alleviating critical shortages of professional personnel in certain areas affecting research teaching and service, and (*c*) facilitating within the student bodies of health-related professional schools the development of knowledge about special areas of disease that have particular significance. The training grant fulfills a dual function. Its funds underwrite certain expenses related to the specific training mission, including the provision of stipends to individuals selected for that training except in (*c*) above. It also serves to create and maintain an atmosphere essential to the training by providing a focal point for the specific discipline or disease within the training institution.

2. *Funds.*—

1959 obligations	$49,812,000
1960 obligations	74,673,000
1961 obligations	109,928,000
1962 estimate	109,756,000
1963 estimate	119,750,000

3. *Present stage of development.*—The nature of the training grants program in each of the seven Institutes and the Division of General Medical Sciences reflects the current status of the manpower situation in the areas for which each has assigned responsibilities. Common to all is a shortage of academicians and investigators. In addition, the various programs are characterized according to specific missions. Thus, most of the pre- and post-doctoral, Ph. D. training grants are administered by DGMS because such training is discipline-oriented rather than categorized according to specific diseases. The remainder are to be found in the training grant programs of NIMH and NINDB and to a lesser extent in NCI, NIAID, and NIDR, where unusual manpower requirements dictate such an activity. The categorical Institutes, however, have primary responsibilities for the postdoctoral research training of physicians in order to provide the blend of specialized clinical and research training essential for careers in teaching and clinical investigation. The severe shortgaes of mental health professionals provides an exception. Although research training is an important component of the total NIMH training grants activity, the primary emphasis is on preparation for careers in service. As mentioned in paragraph 1 above, the necessity of providing special attention to certain diseases at the predoctoral level has resulted in the establishment of the so-called undergraduate teaching grants in cancer, heart, and mental health.

A somewhat similar program is the "chair-side assistant" training grant financed by the NIDR wherein dental students are taught to work effectively with trained assistants so as to improve the quality of dental care and to help stretch the limited supply of dentists.

4. *Plans for the future.*—The recruitment and training of scientists in the fundamental, biological, and medical sciences are required as part of the general effort to expand the scientific competence of the Nation. Indeed, the key to the biological research anticipated in the future lies in the provision of trained manpower adequate in both quantity and quality. Accordingly, the factors cited in support of an expanded research grant program substantiate the necessity for increased training activities. In addition, increased needs for teachers and for personnel for medical services generate supplemental needs for training in specialized fields. The NIH training grant program is an integral and indispensable part of a total national effort to fulfill these needs. In terms of institutional objectives, the training grant is a uniquely valuable means of integrating efforts to deal with specific diseases or discipline problems. Although the characteristics of the program will change in response to changing requirements, such as the emerging needs to recruit scientists at the undergraduate level and to intensify programs for the training of technicians, the basic objectives of the programs will remain constant, and the attainment of these objectives will require an orderly annual expansion of expenditures.

HISTORY OF 1963 BUDGET

Mr. FOGARTY. Another thing we ought to have in one place is tables showing in total for each individual Institute the complete history of the 1963 budget, broken down by activities—what you asked the Department for, what their action was, and an explanation of how it is going to hurt your program, what the action of the Bureau of the Budget was, and how that affected your program.

Can you supply that for the record?

Dr. SHANNON. Yes, sir.

(The requested information follows:)

Chronological development of overall budget for 1963

[In thousands]

Obligations by activity	Original Institute estimate to National Institutes of Health	Change	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	1963 President's budget
GRANTS AND RELATED CONTRACTS							
Research	$621, 664	−$82, 922	$538, 742	−$21, 775	$516, 967	−$45, 128	$471, 839
Fellowships	45, 533	−14, 453	31, 080	0	31, 080	−5, 084	25, 996
Training	166, 290	−30, 290	136, 000	0	136, 000	−16, 250	119, 750
State control programs	18, 500	0	18, 500	−3, 250	15, 250	0	15, 250
Community demonstration projects	4, 000	0	4, 000	0	4, 000	0	4, 000
Total, grants and related contracts	855, 987	−127, 665	728, 322	−25, 025	703, 297	−66, 462	636, 835
DIRECT OPERATIONS							
Research	74, 407	−5, 367	69, 040	−1, 500	67, 540	−2, 140	65, 400
Collaborative studies	55, 085	−2, 585	52, 500	−3, 000	49, 500	−3, 060	46, 440
Biologics standards	3, 369	0	3, 369	0	3, 369	+631	4, 000
Training activities	1, 346	−325	1, 021	−100	921	−89	832
Professional and technical assistance	19, 987	−8, 315	11, 672	0	11, 672	−1, 303	10, 369
Review and approval	15, 525	−374	15, 151	−548	14, 603	−1, 964	12, 639
Administration	4, 239	0	4, 239	−141	4, 098	−213	3, 885
Total, direct operations	173, 958	−16, 966	156, 992	−5, 289	151, 703	−8, 138	143, 565
Total, obligations	1, 029, 945	−144, 631	885, 314	−30, 314	855, 000	−74, 600	780, 400

OVERALL NATIONAL INSTITUTES OF HEALTH—EXPLANATION OF CHANGE

DHEW action.—The major change between the preliminary estimates to the DHEW and the subsequent estimates to the BOB was in research grants. The NIH proposed support for payment of all continuations, supplementals, and an anticipated 80 percent of new grants. The Department approved payment of all continuations and supplementals but maintained new grant support at the estimated 1962 dollar level. In addition, they provided increases over the 1962 dollar level, 24 percent for general clinical research centers, 50 percent for special resource centers, and 29 percent for primate centers. An overhead increase associated with the proposed elimination of the 15 percent limitation on research grants and funding of 95 percent of full direct and indirect costs was provided for projects approved on or after January 1, 1963. Support to heart and mental health State control programs was reduced to the 1962 dollar level.

The changes in the direct operations programs affected opportunities for establishing projects in foreign countries; expansion of the cancer virus and diagnostic programs; preclinical pharmacology program; acquisition of chemotherapeutic agents for clinical trials; and partial support of oversea and domestic establishments for the conduct of international programs.

Budget Bureau action.—Approved payment of all continuations, supplementals, and maintained new grant support at the 1962 dollar level after establishment of the administrative reserve. Categorical clinical research centers and special resource centers were reduced to the 1962 dollar level, whereas, primate centers were provided funds to operate all programs initiated through 1962. Additional funds were provided for increased overhead associated with the proposed elimination of the 15 percent limitation on research grants and funding to a maximum of 20 percent of the direct costs on all grants approved on or after January 1, 1963. Fellowships and training grants were reduced to the 1962 operating level with the exception of an increase approved for mental health service training.

Changes in intramural research affected programs in cancer culture media development, mental health clinical neuropharmacology research center, dissemiination of heart information, dental studies in oral pharyngeal growth and human genetics. Arthritis recently established laboratory of molecular biology, allergy studies in virus respiratory diseases, and neurology satellite operations in universities and hospitals. Reductions in collaborative studies affected the cancer chemotherapy contract program, field studies, and virus studies, mental health biometrics, heart epidemiology, and the neurology perinatal research, biometrics, and epidemiology. Increased funds in biologics standards provides for additional contractual research, expansion of viral vaccine, and animal research programs. Reductions were made in the cancer and neurology professional and technical assistance control programs. Decreases in the review and approval activity relate to the reductions effected in the grants and related contracts area.

GENERAL RESEARCH AND SERVICES

Development of 1963 budget estimates for general research and services

[In thousands]

Obligations by activity	Original Institute estimate to National Institutes of Health	Change	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	1963 President's budget
Grants and related contracts:							
Research	$125, 406	−$14, 456	$110, 950	−$11, 132	$99, 818	+$591	$100, 409
Fellowships	15, 785	−4, 305	11, 480	0	11, 480	−483	10, 997
Training	45, 000	−13, 000	32, 000	0	32, 000	−2, 600	29, 400
State control programs	0	0	0	0	0	0	0
Community demonstration projects	0	0	0	0	0	0	0
Total, grants and related contracts	186, 191	−31, 761	154, 430	−11, 132	143, 298	−2, 492	140, 806
Direct operations:							
Research	0	0	0	0	0	0	0
Collaborative studies	0	0	0	0	0	0	0
Biologics standards	3, 369	0	3, 369	0	3, 369	+631	4, 000
Training activities	0	0	0	0	0	0	0
Professional and technical assistance	0	0	0	0	0	0	0
Review and approval	3, 481	0	3, 481	−505	2, 976	−597	2, 379
Administration	571	0	571	+86	657	−16	641
Total, direct operations	7, 421	0	7, 421	−419	7, 002	+18	7, 020
Total, obligations	193, 612	−31, 761	161, 851	−11, 551	150, 300	−2, 474	147, 826

CANCER

Development of 1963 budget estimates for National Cancer Institute

[In thousands]

Obligations by activity	Original Institute estimate to National Institutes of Health	Change	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	1963 President's budget
Grants and related contracts:							
Research	$99, 684	−$21, 939	$77, 745	−$1, 245	$76, 500	−$10, 670	$65, 830
Fellowships	5, 150	−1, 750	3, 400	0	3, 400	−300	3, 100
Training	11, 820	−2, 320	9, 500	0	9, 500	−1, 720	7, 780
State control programs	3, 500	0	3, 500	0	3, 500	0	3, 500
Community demonstration projects	4, 000	0	4, 000	0	4, 000	0	4, 000
Total, grants and related contracts	124, 154	−26, 009	98, 145	−1, 245	96, 900	−12, 690	84, 210
Direct operations:							
Research	15, 989	−385	15, 604	+958	16, 562	−524	16, 038
Collaborative studies	40, 391	0	40, 391	−3, 000	37, 391	−3, 050	34, 341
Biologics standards	0	0	0	0	0	0	0
Training activities	0	0	0	0	0	0	0
Professional and technical assistance	1, 849	−10	1, 839	0	1, 839	−3	1, 836
Review and approval	1, 955	0	1, 955	+64	2, 019	−284	1, 735
Administration	967	0	967	+22	989	−40	949
Total, direct operations	61, 151	−395	60, 756	−1, 956	58, 800	−3, 901	54, 899
Total, obligations	185, 305	−26. 404	158, 901	−3, 201	155, 700	−16, 591	139, 109

MENTAL HEALTH

Development of 1963 budget estimates for mental health activities

[In thousands]

Obligations by activity	Original Institute estimate to National Institutes of Health	Change	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	1963 President's budget
Grants and related contracts:							
Research	$64, 899	−$5, 277	$59, 622	−$1, 092	$58, 530	−$4, 093	$54, 437
Fellowships	6, 290	−1, 550	4, 740	0	4, 740	−1, 848	2, 892
Training	48, 250	−1, 394	46, 856	0	46, 856	−2, 206	44, 650
State control programs	8, 000	0	8, 000	−1, 250	6, 750	0	6, 750
Community demonstration projects	0	0	0	0	0	0	0
Total, grants and related contracts	127, 439	−8, 221	119, 218	−2, 342	116, 876	−8, 147	108, 729
Direct operations:							
Research	11, 208	−252	10, 956	−920	10, 036	−261	9, 775
Collaborative studies	3, 334	−661	2, 673	0	2, 673	−100	2, 573
Biologics standards	0	0	0	0	0	0	0
Training activities	696	0	696	−100	596	0	596
Professional and technical assistance	2, 681	−559	2, 122	0	2, 122	0	2, 122
Review and approval	2, 600	−285	2, 315	+462	2, 777	−364	2, 413
Administration	672	0	672	+48	720	−29	691
Total, direct operations	21, 191	−1, 757	19, 434	−510	18, 924	−754	18, 170
Total, obligations	148, 630	−9, 978	138, 652	−2, 852	135, 800	−8, 901	126, 899

HEART

Development of 1963 budget estimates for National Heart Institute

[In thousands]

Obligations by activity	Original Institute estimate to National Institutes of Health	Change	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	1963 President's budget
Grants and related contracts:							
Research	$114, 371	−$4, 634	$109, 737	−$5, 062	$104, 675	−$14, 955	$89, 720
Fellowships	5, 100	−650	4, 450	0	4, 450	−835	3, 615
Training	17, 000	−2, 556	14, 444	0	14, 444	−3, 905	10, 539
State control programs	7, 000	0	7, 000	−2, 000	5, 000	0	5, 000
Community demonstration projects	0	0	0	0	0	0	0
Total, grants and related contracts	143, 471	−7, 840	135, 631	−7, 062	128, 569	−19, 695	108, 874
Direct operations:							
Research	11, 648	−1, 106	10, 542	−206	10, 336	−351	9, 985
Collaborative studies	1, 477	0	1, 477	0	1, 477	−147	1, 330
Biologics standards	0	0	0	0	0	0	0
Training activities	500	−250	250	0	250	−64	186
Professional and technical assistance	15, 457	−10, 746	4, 711	0	4, 711	−600	4, 111
Review and approval	2, 580	0	2, 580	−398	2, 182	−224	1, 958
Administration	521	0	521	−46	475	−21	454
Total, direct operations	32, 183	−12, 102	20, 081	−650	19, 431	−1, 407	18, 024
Total, obligations	175, 654	−19, 942	155, 712	−7, 712	148, 000	−21, 102	126, 898

DENTAL

Development of 1963 budget estimates for National Institute of Dental Research

[In thousands]

Obligations by activity	Original Institute estimate to National Institutes of Health	Change	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	1963 President's budget
Grants and related contracts:							
Research	$12, 239	−$2, 443	$9, 796	−$176	$9, 620	−$497	$9, 123
Fellowships	2, 277	−1, 047	1, 230	0	1, 230	−348	882
Training	7, 520	−2, 320	5, 200	0	5, 200	−1, 459	3, 741
State control programs	0	0	0	0	0	0	0
Community demonstration projects	0	0	0	0	0	0	0
Total, grants and related contracts	22, 036	−5, 810	16, 226	−176	16, 050	−2, 304	13, 746
Direct operations:							
Research	3, 273	−56	3, 217	−243	2, 974	−116	2, 858
Collaborative studies	0	0	0	0	0	0	0
Biologics standards	0	0	0	0	0	0	0
Training activities	0	0	0	0	0	0	0
Professional and technical assistance	0	0	0	0	0	0	0
Review and approval	447	−89	358	+123	481	−57	424
Administration	216	0	216	−21	195	−24	171
Total, direct operations	3, 936	−145	3, 791	−141	3, 650	−197	3, 453
Total, obligations	25, 972	−5, 955	20, 017	−317	19, 700	−2, 501	17, 199

ARTHRITIS AND METABOLIC DISEASE

Development of 1963 budget estimates for arthritis and metabolic disease activities

[In thousands]

Obligations by activity	Original Institute estimate to National Institutes of Health	Change	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	1963 President's budget
Grants and related contracts:							
Research	$77, 258	0	$77, 258	−$1, 641	$75, 617	−$6, 863	$68, 754
Fellowships	3, 500	−$1, 700	1, 800	0	1, 800	−623	1, 177
Training	16, 050	−4, 850	11, 200	0	11, 200	−1, 675	9, 525
State control programs	0	0	0	0	0	0	0
Community demonstration projects	0	0	0	0	0	0	0
Total, grants and related contracts	96, 808	−6, 550	90, 258	−1, 641	88, 617	−9, 161	79, 456
Direct operations:							
Research	11, 839	−1, 236	10, 603	−138	10, 465	−292	10, 173
Collaborative studies	700	−50	650	0	650	0	650
Biologics standards	0	0	0	0	0	0	0
Training activities	50	−50	0	0	0	0	0
Professional and technical assistance	0	0	0	0	0	0	0
Review and approval	1, 858	0	1, 858	−364	1, 494	−157	1, 337
Administration	392	0	392	−58	334	−29	305
Total, direct operations	14, 839	−1, 336	13, 503	−560	12, 943	−478	12, 465
Total, obligations	111, 647	−7, 886	103, 761	−2, 201	101, 560	−9, 639	91, 921

ALLERGY AND INFECTIOUS DISEASE

Development of 1963 budget estimates for allergy and infectious disease activities

[In thousands]

Obligations by activity	Original Institute estimate to National Institutes of Health	Change	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	1963 President's budget
Grants and related contracts:							
Research	$56, 472	−$14, 530	$41, 942	−$717	$41, 225	−$4, 080	$37, 145
Fellowships	3, 981	−2, 081	1, 900	0	1, 900	−290	1, 610
Training	9, 750	−3, 850	5, 900	0	5, 900	−550	5, 350
State control programs	0	0	0	0	0	0	0
Community demonstration projects	0	0	0	0	0	0	0
Total, grants and related contracts	70, 203	−20, 461	49, 742	−717	49, 025	−4, 920	44, 105
Direct operations:							
Research	11, 548	−2, 093	9, 455	+913	10, 368	−363	10, 005
Collaborative studies	4, 050	−600	3, 450	0	3, 450	+600	4, 050
Biologics standards	0	0	0	0	0	0	0
Training activities	0	0	0	0	0	0	0
Professional and technical assistance	0	0	0	0	0	0	0
Review and approval	1, 241	0	1, 241	−238	1, 003	−109	894
Administration	374	0	374	−65	309	−21	288
Total, direct operations	17, 213	−2, 693	14, 520	+610	15, 130	+107	15, 237
Total, obligations	87, 416	−23, 154	64, 262	−107	64, 155	−4, 813	59, 342

NEUROLOGY AND BLINDNESS

Development of 1963 budget estimates for neurology and blindness activities

[In thousands]

Obligations by activity	Original Institute estimate to National Institutes of Health	Change	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	1963 President's budget
Grants and related contracts:							
Research	$71,335	−$19,643	$51,692	−710	$50,982	−$4,561	$46,421
Fellowships	3,450	−1,370	2,080	0	2,080	−357	1,723
Training	10,900	0	10,900	0	10,900	−2,135	8,765
State control programs	0	0	0	0	0	0	0
Community demonstration projects	0	0	0	0	0	0	0
Total, grants and related contracts	85,685	−21,013	64,672	−710	63,962	−7,053	56,909
Direct operations:							
Research	8,902	−239	8,663	−1,864	6,799	−233	6,566
Collaborative studies	5,133	−1,274	3,859	0	3,859	−363	3,496
Biologics standards	0	0	0	0	0	0	0
Training activities	100	−25	75	0	75	−25	50
Professional and technical assistance	0	+3,000	3,000	0	3,000	−700	2,300
Review and approval	1,363	0	1,363	+308	1,671	−172	1,499
Administration	526	0	526	−107	419	−33	386
Total, direct operations	16,024	+1,462	17,486	−1,663	15,823	−1,526	14,297
Total, obligations	101,709	−19,551	82,158	−2,373	79,785	−8,579	71,206

Mr. FOGARTY. Mr. Laird?

ANNOUNCEMENT OF RESEARCH GRANTS

Mr. LAIRD. Dr. Shannon, I am interested in finding out what change in policy you have put into effect at the National Institutes of Health in regard to announcing research grants to individual investigators. I have had this called to my attention by many Members of Congress.

I believe some of the problem which you and our committee faces could have been avoided if this matter had been handled properly by the Department of Health, Education, and Welfare, and by the National Institutes of Health.

PROJECT CONDUCTED BY DR. HARRY HARLOW

I would like to take one particular case as an example, and perhaps we can develop some other cases which I also have.

A colleague of mine received from the Department information on a grant. This Member of Congress released the information and it has received nationwide publicity. It was the announcement that a very outstanding investigator at the University of Wisconsin, Dr. Harry F. Harlow, would receive well over $1 million in Federal money to conduct certain research.

The announcement made by the Member of Congress identifies the project as being "to research affectional ties between baby monkeys and their mothers." This particular project is a project which we have discussed in this committee. It has been a continuing project of Dr. Harlow for the last 7 years, I believe. I have had an opportunity to follow this program over the period of several years. I discussed the work with the dean of the school of medicine a few years ago when we appropriated funds to establish primate centers.

The first primate center was established at the University of Oregon, I believe. Last year I discussed with the dean of the medical school, and also with the National Institutes of Health, the research grant application that the University of Wisconsin submitted. Also I discussed it with the Director of the Institute involved.

But to get back to Dr. Harlow's current project; this project is not very well described in the announcement that was made. I have complete sympathy with the problem that faced the Member of Congress involved. I realize that in making this announcement he was not familiar with the project and had to rely just on the inadequate information furnished by the Department.

It seems to me that, if you are going to have Members of Congress announce research grants, it is incumbent upon the National Institutes of Health, the Public Health Service, and the Department of Health, Education, and Welfare to prepare these announcements for the Members who are not knowledgeable on the particular research project involved. Otherwise things get misinterpreted and distorted with the result that you and our committee get ridiculed and blamed for wasting money.

I don't mind being ridiculed by my colleagues up on the floor when I can answer them. But I am quite certain that many, many people who read the news stories ridiculing this project, will never get the correct information about it. Stories like this do medical research irretrievable harm. This is a great embarrassment to the investigator involved.

I don't think we ever want to get into the position where these research grants are made or denied, not on the basis of the ability of the investigator, but because of congressional involvement.

I think it will hurt the program in the long run if this thing isn't handled in a much better manner than it has been this past year.

What change in policy has come about that would create this problem which has gotten so many Members of Congress—and perhaps you have seen the statements of Representatives and at least one Senator after this announcement was made and national publicity was given to it. These people, of course, made their statements on the basis of the very incomplete information which was furnished to a colleague of mine.

Dr. Shannon. Mr. Laird, first may I say that, insofar as it is possible, I share your embarrassment. I also share the embarrassment of Dr. Harlow, who is beyond any doubt one of our outstanding investigators.

PROCEDURE FOR MAKING GRANT ANNOUNCEMENT

I should like to ask Dr. Price to discuss the mechanics of the announcements as they exist today and some of the things that have happened during the past year because these are handled out of Dr. Price's office and you will get direct information from him instead of second hand from me.

Will that be agreeable to you, sir?

Mr. Laird. Yes.

Dr. Price. Mr. Chairman, I would like to describe as a preliminary the nature of the relationship which we as an administering agency have with the applicants for these research grants.

We consider that the information which is provided to us in the application is privileged information, in view of the fact that the individual bares his very private thoughts about the way in which he will pursue his investigation, and gives a great deal of information which has not reached the stage where he is willing to have it published abroad.

Consequently, we have a very limited amount of information at our disposal, beyond the name of the applicant and the general title of his project, which we feel at liberty to use in any public way.

In addition to this type of information, each applicant provides a statement of research project which is to be filed with the Science Information Exchange in the Smithsonian Institution to make this brief description of his work available to other agencies which administer grant programs so there can be a general exchange of administrative knowledge about the work.

This is a very useful device, but it was not designed to provide a statement about the project for public relations purposes.

RESPONSIBILITY OF APPLICANT AND INSTITUTE FOR SUPPLYING INFORMATION

Over the years since our research grants program began, we have adopted the following practice: That the applicant and his institution ought to be the primary source of information about the nature of the work to be supported under the grant so that the invesigator could release as much information as he felt was justified and so that he would have the optimum opportunity to describe his project in the way that he felt would best meet his own requirements from a public relations standpoint.

We have been very loath to put ourselves in the position of becoming the source of this type of information, which is of a scientific program sort rather than primarily the reporting of our stewardship as a Government agency and spending the funds which have been provided.

In addition to leaving with the institution the principal responsibility for releasing notices of this kind, we have published annual listings of awards. We have published summary news releases that indicated that, during a preceding month, we have done such-and-such an amount of business; and this has been summarized by Institute, and we have published for use by news media, if they desire, listings by State and institution summarizing the number of grants and the amounts of money provided to those institutions in the current period.

We have always had a certain number of special inquiries from Congressmen about the fate of particular projects that have been brought to their attention. These we have dealt with on an individual basis, supplying information which had been requested—not, however, for the purpose of providing a basis for a press statement to emanate.

Within the past year there have been a number of questions raised as to whether we were going far enough in providing information which would get to the grassroots and provide people in individual communities with a full knowledge of what their tax money was doing in the support of science in their own areas.

Mr. LAIRD. Were these questions raised by members of the Interstate and Foreign Commerce Committee or the House or Senate Appropriations Committee? Where are these questions raised?

Dr. PRICE. Where these questions may have originally been raised, I do not know. But they came to our attention through officials of the Department of Health, Education, and Welfare.

PROCEDURE FOR CONGRESSIONAL NOTIFICATION

We have been engaged over a period of several months in attempting to devise a method of notification of Members of Congress which would provide information that would meet what was considered to be this need without at the same time violating any of the principles of relationship between us as a granting agency and the applicants.

You asked specifically what change may have taken place in procedures during the past year. This study of the problem has led to the development of a new procedure which has now been placed in effect, which for certain classes—primarily those that are large and of an institutional nature such as the institutional grants, demonstration grants, and construction grants which have always been——

Mr. LAIRD. Construction grants have always been handled on a different basis. I don't want to get into the area of construction grants. I would like to limit our discussion here to the scientific research grants to individual investigators.

That is really what I am interested in.

Dr. PRICE. The type of grant that you refer to comes nearest to being dealt with under this new procedure under the title of "Program Grant," where a large and fairly broad program of investigation under the supervision of a principal investigator—ordinarily a group effort of a number of investigators in an institution—is dealt with.

Mr. LAIRD. I really look at this problem of bricks and mortar a little bit differently than the problem I am trying to direct these questions to.

Dr. PRICE. I included it only because it is one of the categories of grants that are involved in this new procedure for notification. The procedure which has now been adopted is one that, as soon as the administering agency has determined to award a grant, information as to the name and address of the recipient, the project number, the congressional district if it is known to us, and the amount of the award, and the descriptive title of the project will be provided to the Congressional Liaison Office of our Department for notification to the appropriately interested Congressman.

Then 24 hours after the information has been provided to the Congressional Liaison Office, the operating agency will send a notification to the recipient indicating to him that this application has been granted.

In those cases where the award is considered to have some general news value, the operating agency is instructed to establish a release date and coordinate the information with the appropriate grantee institution, and then arrange for transmission of a press release through our Department's press office at the same time that the award information is made available to the Congressional Liaison Office.

This, in summary, sir, is the change which has taken place in the notification procedures which we are following.

Mr. LAIRD. This has just gone into effect this past year?

Dr. PRICE. Yes, this procedure has just gone into effect. We have been developing it for a period of, I would say, about 4 or 5 months.

Mr. LAIRD. Do you have any limits on the size of the the grants concerning which you are notifying Members of Congress?

Dr. PRICE. We have set a general limit of $200,000 on the grants which will be incorporated.

PRESS RELEASES

Mr. LAIRD. In the case that you spoke of where you prepare a press release, this press release is prepared by your press office?

Dr. PRICE. Where a press release would be prepared under this procedure, it would be prepared by the Information Office of the Institute involved.

Mr. LAIRD. This press release is one that the National Institutes of Health puts out under its name. Is that correct?

Mr. KELLY. By the Department's press office.

Mr. LAIRD. Do you make available in advance a copy of this press release so a Member of Congress, in drawing up his own press release, gets the full information about the project?

Dr. PRICE. If there were a press release, I am sure that it would be made available to a Member of Congress, yes, sir.

Dr. SHANNON. Mr. Laird, I think you realize that the Harlow grant would not be considered of a type for which a press release would normally be prepared. The latter are really the very large, very broad program grants. These are not ordinary project grants.

NEED FOR BETTER INFORMATION

Mr. LAIRD. My problem is, if you are going to carry through with this procedure, how can you get better information to the Members who are advised of these project approvals?

That is up to you to decide. That isn't up to us to decide in our committee. The thing I want to get at is: If you are going to get into this business as you seem to want to do, then you have got to be in a position where this thing doesn't come back and cause us the problems that it already has and that I think I can see in the future.

Dr. TERRY. Mr. Laird, may I ask Mr. Kelly to make some comments on this? He has been involved in some of our discussions and determinations.

Mr. KELLY. May we go off the record a moment?

Mr. LAIRD. I think we ought to have most of this on the record. All right; go ahead.

(Discussion off the record.)

Mr. FOGARTY. On the record.

Mr. LAIRD. Dr. Shannon, I understand in this particular case—and I hate to belabor this, but this is one that has been given quite a bit of publicity—the Member of Congress involved has asked the Department of Health, Education, and Welfare to notify him on all grants—a blanket request to be notified on all grants involving his congressional district.

This notification, in this particular case, was made in response to this blanket request for notification?

Dr. SHANNON. This is correct, sir.

Mr. LAIRD. My concern, Dr. Shannon, is that the kind of information which you made available to the Member of Congress was not sufficient for him to adequately announce this particular project. I believe as a result this has directly contributed to the misunderstanding that has existed and has snowballed all over this country about this investigation being carried on by Dr. Harlow.

What is your opinion?

PROBLEMS OF PREPARING PRESS RELEASES ON EACH GRANT ACTION

Dr. SHANNON. I think your statements are completely correct. We did not furnish the type of information that could lead to a reasonable news release describing the program in layman's terms. I might point out that the request we complied with was not for such type of information, but simply for information about actions taken that affected grantees in a given congressional district.

These actions are very many, and had we known that the Congressman wished to issue some press releases, I believe our advice would have been that he do this in association with the grantee, who would have full knowledge of the total scope of his program, the setting in which it is performed, and how the program can best be described in both objective and understandable terms.

It is theoretically possible for us to develop this type of information, but only with some difficulty, because the setting of the experiment is an institutional setting and certain factors that determine its significance to the institution are not known to us.

But I must say that in respect of any very large investigative operation such as is conducted by a university it is impossible for us to produce that type of information for each grant action we take throughout the year. Moreover, we cannot make available for publication the information that is available to us without violating a confidential relationship that is established between us and the investigator when he applies to us for a grant.

We have been unwilling, quite frankly, sir, to develop any press release on any subject without the concurrence of the investigator who is involved, because we feel he has special privilege with regard to that information.

As soon as we begin to interpret what he chooses to do and how this fits into his research pattern, we feel we are invading his rights. So I don't believe it would be possible for us, short of consultation with each of our grantees involved, to prepare a suitable press release that could then be used for whatever purpose the Congressman wished.

I may be looking at this too rigidly. Dr. Price, who has this as his day-to-day concern, might come up with something to the contrary, if he does not agree with this.

Mr. LAIRD. I would like to hear from Dr. Price about his personal opinion.

Dr. PRICE. I agree very strongly with what Dr. Shannon has said. In the first place, we have a volume problem, which I think would be completely defeating any objective of this kind if there were not other more important objections to it.

In the first place, we have some 20,000 awards a year. While a great many of these are very small and attract very little notice, in the local area involved they may be as interesting and important as a $200,000 project may be in one of the larger centers.

Consequently, we feel that it would be impossible to embark on an attempt to interpret each one of these individually.

But of much greater importance to me is maintaining the relationship which we bear to the grantee in relation to the intimate details of his work and his own privilege to report these to his colleagues and to interpret them to the public.

I would be very loath to see us as an administering agency involved in attempting to give this kind of an interpretation of an investigator's work.

I feel strongly that we have a responsibility to make a public accounting of the general use to which these funds are put. But in terms of attempting to interpret the details of the projects which they support, I feel that we would be on very shaky ground in attempting to do it.

I think that we would find that we would frequently be in exactly the same embarrassing situation that a Member of Congress might be who attempted to become the source of this type of interpretation.

Mr. Laird. I know as a member of this committee that goes over a lot of these various projects that you have, on both sides of the aisle here we have tried to avoid as much as possible, particularly in the House, becoming project officers.

I think if we put ourselves into the position of being project officers on these grants and give the impression to the scientific community that we are exercising any kind of influence on a particular grant, I think we would be in some trouble.

I think you have to do this on a broad general basis rather than a specific grant basis. I think there are real pitfalls involved in this procedure if you can't follow through and give them complete information.

COMMENTS OF THE SURGEON GENERAL ON INFORMATION RELEASES

What is your comment on this, Dr. Terry?

Dr. Terry. I would certainly have to sanction everything that has been said here, sir. I think basically what it amounts to, if one tries to translate it into practical terms, is that if a Congressman is making an announcement of some such grant, the only source from which he could get reliable information and not place us in a position of having violated a confidence is from the university and from the individual grantee.

Since this incident has arisen, I have wondered about the possibility: Is there any possibility that we might be able to get the Members of Congress sufficiently cognizant of this aspect so that their staff, before they attempted to announce such actions, could coordinate it with the individual grantee?

DISCRETION IN MAKING ANNOUNCEMENTS

Mr. Laird. I know I have been notified that a grant was made in my congressional area. I stayed completely away from it because I thought if I announced this and it was in my local paper, it would take credit away from the investigator. He had gone through this long procedure of going to a study group and through the Council and gotten approval from the Surgeon General on the basis of the application he made.

I felt it would take away from the recognition that he deserved if I released the information to the press. So I just kept very still about it.

I have announced sewer projects and buildings and things in that area—airports and post offices. But this is different. Here you are dealing with a scientific project grant made on the basis of the ability and imagination of a scientist, not on the basis of anything a Congressman has done.

Ths is, I think, a very serious problem. I am not complaining about having to answer the mail on this or answer to my colleagues. That can be taken care of. I can do that without too much trouble. But I wonder about some of these investigators, how they are going to feel about it. What do you think their reaction would be generally throughout the country to this procedure?

Dr. TERRY. I think this one incident in itself is embarrassing enough. I think it has unfairly reflected on the investigator, his institution, the Congress, the Public Health Service, the Department, and the whole NIH.

I think the publicity which it has gotten has been most unfair to all persons who have been involved.

CONGRESSIONAL RELATIONSHIPS

I would like to say at this point, Mr. Laird, that we in the Public Health Service, in the Department, have been very proud of the relationship which has existed over many years between the Congress and our programs. We have been very appreciative of the tremendous interest that the Congress has taken.

Even more than the interest in terms of support, I think we have valued the respect that the Members of Congress have shown for our programs in terms of not trying to apply political influence in a determination of these grants. We have been completely free of this problem, which could conceivably develop. It has been a matter of mutual respect between the Members of the Congress and our programs.

I think it is most unfortunate when anything develops in such a way in relation to these activities which would tend to indicate that this grant was made because of any political influence. I say flatly that it isn't true, and I think that anything in that direction or anything which might be conceivably implied or interpreted in such a way that it would reflect such an opinion or an attitude would be unfortunate for all of us.

Therefore I certainly share your concern that you have expressed, and I am deeply embarrassed and humiliated about the type of publicity which has been associated with this individual grant.

JOINT INVESTIGATOR—NIH STATEMENT

Mr. KELLY. I wonder if I could suggest, Mr. Laird, that, inasmuch as you have brought this one up and inasmuch as the publicity associated with this grant has made it appear that the Federal Government is wasting funds——

Mr. LAIRD. I want to get into this and develop this now.

Mr. KELLY. I was going to ask that, inasmuch as Dr. Price has brought out that they prefer that the explanation of a project and its value and what they hope to develop can only be truly worked out effectively with the investigator concerned, the National Institutes of Health might get together with Dr. Harlow and prepare a statement that describes the work that has been accomplished by this investigator and the work that is intended to be accomplished and its purpose so that a complete statement of the value of this project could be inserted in the record?

Mr. LAIRD. Dr. Shannon, I believe the suggestion is a good one. I would certainly appreciate it if you, as Director of the National Institutes of Health, and Dr. Felix as the Director of the Mental Health Institute, and Dr. Harlow get together and prepare a statement which we can insert at this point in the record, explaining this project in some detail, setting forth the progress that has been made during the past 7 years, and the projected program for the next 5 years under this grant.

Dr. SHANNON. This we shall be glad to do, sir.

(The requested information follows:)

Dr. Harry Harlow, professor of psychology at the University of Wisconsin, has conducted extensive research involving rhesus monkeys since 1934. He has built one of the best primate laboratories in the country, where by studying the behavior of these animals, he has been able to explore problems which cannot be investigated directly in human subjects.

RELATION BETWEEN ANIMAL-AND HUMAN RESEARCH

In the subhuman primates, the structure of the brain and the nervous system is the most developed of all animals and comes closest to that of man. Therefore, it becomes particularly meaningful to perform relevant physiological and anatomical studies on these animals when we are looking for clues to some of the more obscure aspects of the structure and function of the human brain.

Behavior studies with monkeys are also significant. They can shed light on those aspects of human behavior which are similar to behaviors found in primates other than man and they can help to detail those aspects of human behavior which are unique to man. On both levels, they are a vehicle for comparative studies which can be expected to result in a much better understanding of complex human behavior.

The results of studies on monkeys cannot, of course, be translated directly to conclusions about human beings, but they can provide, and have, many new ideas for investigations on the human level. Conversely, studies of human beings have raised problems which can be studied most effectively with animal subjects.

IMPLICATIONS FOR MENTAL HEALTH

Thus, the National Institute of Mental Health does not support Dr. Harlow's work because we are especially interested in the study of monkey behavior itself, but because we are very interested in the implications which these studies may have for a deeper understanding of human behavior. For example, there is general agreement among mental health practitioners that the nature of the mother-child relationship is critical in the development of a child's ability to establish healthy and satisfying interpersonal relationships. There is some reason to believe that it has significant effects on the development of perceptual and intellectual function also.

Systematic evidence on these questions, based on rigorously controlled studies which explore all aspects of the problem, is difficult to obtain. For ethical reasons, such investigations often cannot be undertaken with human subjects. Certainly, we cannot experiment on human mothers and their children to see what kinds of behavioral disturbances the experimental changes will produce in the child as it grows up. We cannot experiment directly with factors likely to induce mental retardation in children. But we can do these things with animals. The information collected in this way is extremely important in suggesting new theoretical approaches to problems of mental health and in testing old ones. It is an essential supplement to research performed directly on human subjects and paves the way for new and better human research.

MOTHER-INFANT STUDIES

Among Dr. Harlow's behavioral investigations, those concerned with the effect of mother-infant relationships on the future development of the animal have occupied a central position. He has developed novel procedures in these studies, including the use of "artificial mothers," which have shown that the experimental control of the physical characteristics of the "mother" can influence not only the social responses of the infant monkey to other infants, but its perceptual and learning capacity as well. Further, these influences are maintained, to a greater or lesser degree, over a long period of time, and have a critical effect on the maternal behavior of the adult female when she has infants of her own. Dr. Harlow has shown that monkeys raised on artificial mothers develop into mothers totally devoid of normal maternal behavior.

His research also demonstrates that monkeys raised in isolation later display social and behavioral abnormalities.

These studies have attracted a great deal of attention and interest from psychiatrists, psychologists, psychoanalysts, and anthropologists. Theories developed by scientists in these behavioral disciplines have suggested that infants deprived of mothers or deprived of a reasonably wide range of social stimulation will not develop normally. At best, it was held, they would demonstrate personality problems; at worst, they might show severe mental illness. Dr. Harlow's research provides partial experimental verification of these theories.

MENTAL RETARDATION

Dr. Harlow is also carrying out critical basic investigations on other facets of infant development, including learning and problem solving; the development of visual exploration and curiosity; the relation of brain physiology to behavior; the effects of brain injury on future development; and the nature of the changes resulting from metabolic disorders. This research may become extremely important in increasing our understanding of some of the problems involved in mental retardation.

No one yet knows the extent to which mental retardation results from metabolic or biochemical malfunction. It has been estimated that as many as 25 percent of the cases of retardation may result from such malfunction. Further they have developed techniques for inducing in monkeys other metabolic diseases, as well as phenylketonuria, known to cause retardation in humans; galactosemia, and disturbances in the metabolism of branched chain amino acids. These monkeys show the typical symptoms of feeblemindedness. Studies of this type provide a promising research tool for experimentation in ways of reversing the mental retardation which results from these metabolic disorders.

BRAIN INJURY

Other studies in Dr. Harlow's laboratory focus on the effects of brain injuries, such as may be suffered at birth. These investigations are concerned with the effects of brain injuries on all aspects of development—neurological, intellectual, and affectional. This research can be expected to produce important information regarding mental retardation. But, it may also produce significant leads on the baffling problem of childhood schizophrenia.

ENDOCRINE STUDIES

Dr. Harlow and his associates are also conducting hormonal studies related to problems of reproductive physiology, with special emphasis on finding ways of maintaining pregnancy in mothers who habitually abort their young. Some preliminary success has been achieved through the use of endocrine substances, but the use of these compounds has resulted in some undesirable side effects. A search for a safe and effective compound is under way by means of detailed investigation of the effects of these compounds on both the mother and the infant. Further study to determine the response of the monkey infant to standard tests of endocrine function and a comparison of these responses with those observed in the human infant is in progress. If a close similarity is observed, the monkey will provide a convenient tool for the study of possible diagnostic procedures and methods of treatment for various endocrine disturbances, which can not now be tried with human infants.

Thus, Dr. Harlow's investigations have provided many significant leads for further studies with humans. They have suggested possible interpretations of data previously obtained with humans, and they can be expected to continue to produce such results.

PROFESSIONAL AND SCIENTIFIC BACKGROUND

Dr. Harlow has vigorously pursued a distinguished academic and research career for over 30 years. The value of his scientific work has been recognized in many ways; the following are but a few of them. He has served as chairman of the Department of Psychology at the University of Wisconsin, where he holds the rank of full professor; he is a member of the Army Scientific Advisory Panel in the Office of the Secretary of Defense; and he was president of the American Psychological Association in 1947–58. He has published extensively in the scientific literature and has served as the editor of the Journal of Comparative and Physiological Psychology since 1951.

In 1960, Dr. Harlow received the "distinguished scientific contribution" citation of the American Psychological Association, which carries with it a $1,000 award. The citation is an indication of the attitude of his fellow scientists toward Dr. Harlow's work and states, in part: "His indefatigable scientific curiosity has opened up new areas of research in animal behavior * * * his unswerving devotion to fact, observation, and experiment has given his contribution an integrity of inestimable value to scientific research in psychology."

Dr. Harlow's research findings have substantially helped to advance scientific knowledge toward the ultimate goal of salvaging human lives which are now crippled by distortions in maturation and development. His research program represents a multiple attack on the problem—both physiological and psychological, concerned with both structure and function. He has referred to his research as a "baby saving" program. He may well be right.

Mr. LAIRD. I believe Dr. Harry F. Harlow to be one of the outstanding medical research investigators in the country. Wouldn't you agree?

Dr. SHANNON. I agree completely, Mr. Laird.

Mr. LAIRD. You are in a better position to judge that than I am, by the way.

GRANTS TO FOREIGN COUNTRIES

In this budget which is before us, Dr. Shannon, there is an increase in grants to foreign countries. It seems to me that the factors involved in the administration of grants-in-aid for research to foreign nations is more complex and much more expensive than similar grants made to people within our own country.

In many cases I am afraid these grants can lead to misunderstanding between countries. You are expanding this program this year. Most of the grants are made to the so-called developed countries rather than the developing countries.

GUIDELINES FOR FOREIGN GRANT

Dr. SHANNON. Yes, Mr. Laird. If I may, I should like to submit for the record at this point the guidelines under which grants are currently being made to applicants outside of the United States. Then I should like to comment on some of the points in these guidelines.

(The additional information referred to follows:)

FEBRUARY 12, 1962.

INTERNATIONAL RESEARCH ACTIVITIES OF THE NATIONAL INSTITUTES OF HEALTH

INTRODUCTION

The mission of the NIH is to advance the health of the American people through medical research and through support of medical research and research training. Recently, U.S. scientists have assumed world leadership in this field; however, more than anything else we owe our health, and thus to some degree our national strength, to the past accomplishments of foreign medical science. This very crucial national resource, our health, will depend more than anything else on the combined efforts of U.S. and foreign medical scientists. Furthermore, the efficiency with which foreign and domestic scientists collaborate in their attempts to study and control disease will depend in part on the initiative exercised by the United States. This does not mean, of course, that the United States should assume the entire or even the major share of responsibility for the support of medical research. However, it does indicate that the advancement of medical sciences in the United States and the advancement of the medical sciences abroad are interrelated and interdependent.

Thus, American scientists contribute to and benefit from the work of foreign scientists.

Our foreign research activities allow us to bring to bear the talents and skills of highly competent foreign scientists on the health problems of the United States. Thus, NIH is now taking advantage of a vital resource which otherwise would not be available.

I. LEGISLATION

The Public Health Service has engaged in international research and training activities under basic authority provided the Surgeon General in section 301 of the PHS Act of 1944 and by Public Law 86–610, 1960.

The International Health Research Act of 1960 was enacted in July of 1960. This legislation provided for the first time an explicit expression of the will of Congress in respect to the support of health research overseas, although it added little in the way of new authority. Two major purposes of the legislation were cited:

1. To advance the status of the health sciences in the United States and thereby the health of the American people through cooperative endeavors with the other countries in health research, and research training; and
2. To advance the international status of the health sciences through cooperative enterprises in health research, research planning, and research training.

Significantly, the responsibility for the achievement of these two objectives was separated. The responsibility for achieving objective No. 1—advancing the status of the health sciences in the United States through oversea research activities was given to the Surgeon General and the Secretary of HEW. The responsibility for objective No. 2—advancing the international status of the health sciences was given to the President. The law indicates that he may delegate this authority to the Secretary of HEW who may then in turn delegate it to the PHS.

This clear distinction between the role of the Secretary and the Surgeon General and that of the President under this act in terms of the purposes to which support of health research overseas is to be directed is most significant. It clearly reinforces the concept of NIH objectives set forth below. The intent of Congress to distinguish between action in support of national objectives and action aimed at broader international objectives is clearly evident.

II. PHILOSOPHY

NIH is part of a larger community of agencies and organizations involved in international health activities. We may support or conduct research by delegation of authority from these agencies. We may participate in the actual support of research and research training based on the statutory provisions of our own legislation. In either circumstance, our role is primarily related to our scientific mission.

Although research support programs may influence or affect the conduct of foreign policy, the NIH international research program is not designed for this purpose. Thus, a clear distinction must be drawn between technical assistance (foreign aid) and support of research abroad for domestic or national purposes.

The assessment of foreign research support by NIH must consider the aggregate effects on science ecology within a given country, as well as the scientific merit of all individual research proposals. The size, scope, and duration of research commitments may innocently disturb seriously the plans and aspirations of a foreign domestic research program. Therefore, action to support research abroad should be taken only after careful consideration of all circumstances involved.

The rapid growth of NIH support of research abroad through research grants from a level of $100,000 in 1955 to $8.4 million in 1961, provides sufficient justification for concern that in certain instances, NIH foreign grants may affect significantly the overall development of health programs abroad. The NIH contribution to research abroad should be provided in such a way as to insure that it will be additive rather than a replacement for existing local support. Since the nature, scope, and magnitude of the U.S. effort in international health science have been incompletely assessed and evaluated, we recognize the importance of carefully confining our responsibilities within our specific statutory authorizations. Thus, NIH recognizes that the primary responsibility for certain other international scientific and health activities, such as the development of medical education, rests elsewhere.

III. OBJECTIVES

The NIH provides grant support for biomedical research performed by foreign scientists when it is expected that the results of such studies are likely to advance the status of the health sciences in the United States as well as the country of the applicant. Research which is relevant to a specific NIH program may be supported by contract or by research agreement.

The Office of International Research is responsible for establishing mechanisms adequate to assure that the general policies and specific criteria governing the NIH international programs are applied effectively and economically.

This mechanism should be adequate to assure that all research applications are reviewed, preferably on the scene, by a person or group having the full confidence of NIH. Reviewers may include study section or council members, U.S. scientists with personal knowledge of applicants and their institutions, foreign scientists in whom NIH has confidence, or NIH staff members.

Preliminary review should take into account the ability of the scientist, the worth of his proposal, the environment within which he works, and, when appropriate, the total content of the Nation's effort in the medical sciences.

IV. CRITERIA FOR FOREIGN AWARDS

The NIH will accept for scientific evaluation and review research proposals which meet both the following criteria:

(1) The research proposed is outstanding, or original in concept, or would utilize the talents, skills, materials, or other resources not likely to be available in the United States; and

(2) The proposal is of such a nature that the results are likely to advance significantly the status of the health sciences in both the country of the applicant and the United States.

V. MECHANISMS

Whenever possible, the existing mechanisms of receipt of applications and the scientific and administrative review of research proposals will be the responsibility of the Institutes and Divisions involved. However, those international program areas which go beyond the responsibilities and interest of a single Institute and which relate to NIH as a whole become the responsibility of the Office of the Director, NIH. The existence of activities and problems of this nature (in large measure resulting from the need to inform and clear international research developments with many other elements of PHS, Office of the Secretary, HEW, Department of State, etc.) have led to the establishment of a coordinating Office of International Research. In order to perform these functions as well as to facilitate program analysis and budgetary planning, the following functions are performed by the Office of International Research, Office of the Director, NIH:

This Office is responsible for coordinating all international activities of the National Institutes of Health. It advises the Director and the Office of the Surgeon General on matters relating to the international aspects of medical research and research training, and assists the Institutes in development of international programs. It is specifically responsible for administration of the NIH Public Law 480 program and coordinating Institute proposals for research under this program in foreign countries. The Office constitutes the central point within NIH for relationships with the World Health Organization, the Pan-American Health Organization, and other international research and scientific organizations. The Office is comprised of an Office of the Chief, a Foreign Grants and Awards Section, a Special Foreign Currency and Program Services Section, and a Program Analysis Section. The Office is also responsible for establishing and administering NIH oversea offices.

This Office will provide a mechanism whereby the National Institutes of Health can work with international organizations, foreign institutions, and scientists on a planned, predictable long-range basis.

The OIR, in collaborating with the Institutes, will be responsible for an organized systematic assessment of medical research potential and research resources in foreign countries. This will facilitate the implementation of direct (intramural) conduct of research overseas by NIH as well as providing information for study sections and advisory councils in their review of foreign grant applications.

Dr. **Shannon**. Over the years we have made grants overseas primarily to take advantage of exceptional or unique opportunities that do not exist in this country. A grant is deemed suitable for payment, first, if it has direct relevance to the domestic mission of one of our Institutes; second, if it is characterized by more than ordinary excellence as compared to the run-of-the-mill grants in this country; and, third, if it takes advantage of a rather unique or unusual opportunity which is not generally available in this country.

When you put these three criteria together, it means that basically we are talking about areas of advanced science in these countries rather than about the use of research funds to aid in the development of the country.

SCOPE OF FOREIGN RESEARCH GRANT PROGRAM

This program, which began very small in the early fifties, last year amounted in research grants to $8,374,570.

With the encouragement of the Congress, and as a result of the growing awareness of the role of the United States in the support of science generally and more particularly the medical sciences, this program has about doubled at 2-year intervals.

In addition to continuing surveillance, we began inquiring carefully into grants in foreign countries about 2 years ago. As a result of information we had last summer, we came to the conclusion that we should regear our total operations in the international field and adopt more rigid, even more restrictive criteria for acceptability than had been obtained in the past.

With full information now developed, we are looking forward to a meeting on February 23 of our intercouncil committee in association with the advisory committee of the Office of International Research in order to develop firm guidelines for action by the Councils in developing their advice to the Surgeon General on specific grants.

We feel that there are certain things that can't be done here that should be supported overseas. There is no doubt that such activity should be supported—for example epidemiological studies or studies in very unique laboratory facilities, and the like.

There are other studies that can be done equally well in the United States and overseas. Some of these are of such an importance that, in order to increase the effectiveness of work in a given area, they should be supported both domestically and overseas.

One of the side effects of U.S. research grants overseas, which is now becoming apparent, is that these grants have stimulated the development of medical science overseas. However, unless we recast the guidelines for our oversea operations, we shall run the danger of assuming obligations that would be abnormal.

So we shall probably recast our present guidelines and further emphasize one of the mechanisms that has always been available to us; namely, collaborative research. We shall be glad to report to the committee the results of this meeting, which will be held before the committee closes its books on this hearing, if this will be helpful.

PARIS NIH OFFICE

Mr. LAIRD. Dr. Shannon, quite recently the National Institutes of Health, in expanding its program, appointed a very capable person, Dr. Charles B. Hutterer, to be in charge of your oversea office which you have established in Paris.

Dr. SHANNON. Yes, sir.

Mr. LAIRD. How long has that office of NIH been open in Paris?

Dr. SHANNON. I would say approximately 2 months.

CONSIDERATION OF ECONOMIC LEVEL OF COUNTRIES RECEIVING GRANTS

Mr. LAIRD. In going over the projects that have been approved in the various Institutes, it seems that increasing amounts of funds are being made available to countries that are in pretty good financial shape.

Dr. SHANNON. Yes, sir.

Mr. LAIRD. There is a real doubt in my mind of the need for increasing funds for foreign research in these countries that are capable of financing their own programs. Some of them are in a financial position that is sounder than our own Government.

I think you are familiar with the fact that the Germans, probably within the very near future, will reevaluate their currency in connection with ours. The Italians are going to reevaluate the lira in connection with the American dollar, indicating a strong position for the currency of many of these countries as they relate to the American dollar.

Most countries with competent investigators that are available to carry on this work happen to be the prosperous countries. It seems that they can afford to support the research programs in the medical area, whereas the developing or, as some people refer to them, the underdeveloped countries lack competent investigators to conduct research.

Most of the underdeveloped countries have little potential for supportive research in cancer, mental health, cardiovascular diseases, and so forth.

It seems to me that their present needs for research are along the lines of more food, better housing, and simple hygiene. There may be a few exceptions to this. I would like to get your comments in regard to this underlying philosophy in making these grants.

Dr. SHANNON. Mr. Laird, perhaps I can express my basic philosophy in terms of the actions we have taken during the past year and what we shall propose to this committee of consultants late in February.

When we completed our analysis last summer, we stopped making new grants overseas, awaiting an overall assessment by our advisers. From grants that had already been made but had not yet been put into effect we removed the overhead item so that, at the very least, there would be financial participation by the grantee institutions to the extent of 20, 30, or 40 percent of the total cost of the research rather than full NIH support including both direct costs and indirect costs.

We propose to recommend to the advisory group that the dollar value of grants in advanced countries not be increased beyond the level that currently obtains; and that over a period of 2, 3, or 4 years this amount be progressively reduced, in some countries, and that independent grants be replaced, where possible, by work that is truly collaborative in nature.

I can't predict what the members of the advisory group will say. I think that in general, they will be of a mind to accept these general recommendations—although some of them, I am quite sure, will say that the purpose of the research dollar is to acquire knowledge pertaining directly to our domestic objectives and if this can be done more effectively overseas than domestically, then let's spend at least a portion of our funds overseas.

I happen to feel that support of research has a twofold effect. It acquires knowledge and it has some impact on the economy of the country concerned. I may say I am sure that when the advisory group meets with us in the latter part of February they will recommend some modification of our program perhaps along the lines I have just summarized.

I have very strong feelings on this, sir, and I believe that the advice the Surgeon General will receive will not be very different from yours.

INTERNATIONAL CENTERS FOR MEDICAL RESEARCH

Mr. Michel. Dr. Shannon, closely akin to this subject on what we are doing in the international field, I see here the amount of $2,984,000 will provide support for international centers for medical research and training. Just what does this involve?

Dr. Shannon. That is quite a different thing. This is to provide support for five universities in the United States—to provide them with an oversea base for the conduct of research of importance to the United States, and to provide a training area so that a portion of our medical scientists have broad experience overseas as well as at home.

Mr. Michel. What are those five?

Dr. Shannon. The University of California, Tulane University, Louisiana State University, Johns Hopkins, and Maryland.

GENERAL CLINICAL RESEARCH CENTERS

Mr. Michel. Of those 40 general clinical research centers, do we have in the record where those are located?

Dr. Shannon. We can place them in the record.

Mr. Michel. Would you put those in the record?

There are 20 more contemplated in 1963. Have those sites been chosen?

Dr. Shannon. We can place them in the record.

(The information may be found beginning at p. 944.)

Mr. Michel. That is all.

WORLD HEALTH ORGANIZATION ACTIVITIES

Mr. Laird. Dr. Shannon, back several years ago the World Health Organization authorized a program in medical research. In the 1962 budget the amount of $500,000 was approved as the U.S. contribution to this program.

I recently received a report on this program and I find that, of the 97 members, the only country in the world that has contributed a single dollar to that program is the United States of America.

At the time it started I felt that this program had some merit. But I don't believe it can have very much merit if the 97 other members of the World Health Organization don't think enough of it to contribute a dollar.

As we look over the 1963 budget, and I realize this doesn't come in your part of the budget, I see that this same set of circumstances faces us in 1963.

Dr. SHANNON. Mr. Laird, that is not the whole story. The WHO budget is quite complex. I have not seen the 1963 proposal myself yet but they started a program of increasing the research item in the regular budget by $250,000 a year.

Mr. LAIRD. To which we contributed.

Dr. SHANNON. To which we contributed, yes, sir. They stopped last year at the specific request of the United States that they blanket into the regular budget the total malaria eradication program to which you know we also contributed.

Mr. LAIRD. Of which we contributed the major portion of the cost.

Dr. SHANNON. Yes, sir. It is my understanding that they propose to increase the regular budget by a quarter of a million dollars a year, under the assumption that eventually they will support the bulk of their medical research out of their regular budget.

I talked to Dr. Candau about this in about the same terms that you have used. His basic attitude, as he discussed it with me, is that, until they have the malaria eradication program on a sound stable base on a regular budget and without special funds from special programs, they are not in a good position to solicit funds for medical research as such.

But he does look forward to a progressive increase in the support of research through the regular budget. I personally feel this is not increasing rapidly enough but, Mr. Laird, medical research is only a small part of the total activity of the World Health Organization.

U.S. CONTRIBUTIONS TO WORLD HEALTH ORGANIZATION

Mr. LAIRD. I realize we are making our contribution to the regular activities, too. But in the report which I got from the State Department, the medical research portion of that world health program is still being supported 100 percent by the United States.

This has been going on now for 4 years, because when the chairman of the committee and I were in Geneva attending the World Health Organization, this was set up as a start.

Dr. SHANNON. Yes, sir.

Mr. LAIRD. But it was the intention, as I understood it, that the other countries of the world would take part in this activity. We are in the fourth year, going into the fifth, I believe now, in which we find that we are being asked again to carry the entire load for the other 97 nations.

Dr. SHANNON. Mr. Laird, what I should like to do at this point is to determine for the purpose of the record the total funds expended by the World Health Organization, both from the regular budget, from the service accounts, as well as from the contributions of the United States, and summarize this for the purposes of the record.

Mr. Laird. I would also like to have put in the record the cost of the malaria program, and our contribution over the last few years to that particular program.

Dr. Shannon. This I shall be glad to get.

Mr. Laird. Because we have handled that separately, too, through a seperate appropriation from the Congress, and not carried it in the regular budget of the World Health Organization.

(The information referred to above follows:)

The budget of the World Health Organization and U.S. participation therein, calendar year 1961

Item	All contributions, total[1]	U.S. contributions[2]
1. WHO effective working budget (total)	$19,780,448	$5,999,700
2. Special accounts:[3]		
(a) Malaria eradication special account contributed to WHO	4,184,000	4,000,000
(b) Water supply promotion, special fund	189,460	175,000
(c) Medical Research Special Fund[4]	509,670	500,000
(d) United Nations Special Fund[5]	278,250	111,300
(e) United Nations Technical Assistance Fund[5]	5,973,000	2,389,200
(f) Grants for specific research projects		[6] 549,000
3. Pan American Health Organization items:[7]		
(a) Allocation for PAHO	4,767,194	3,102,000
(b) PAHO malaria eradication special account	2,794,504	1,500,000
(c) PAHO miscellaneous	1,635,701	1,082,576
Funds administered by WHO (total)	40,112,227	19,408,776

[1] Data presented in this table are annual budget estimates based on estimated contributions as reported in Official Document No. 113 of the World Health Organization. Actual expenditures for many items may be less than budgeted amounts.

[2] Data on U.S. contributions from State Department.

[3] Funds in special accounts represent a contribution for specific purposes and are in addition to current allocations for the same purposes in the regular budget.

[4] Voluntary contributions for medical research in addition to funds for medical research available through the regular budget and funds obtained from research grants. Total of funds for WHO medical research activities, 1961, estimated as follows:

Medical research in regular budget	$750,000
Voluntary contributions to special account	509,670
Grants for specific research project	549,000
Total	1,808,670

[5] These items represent funds contributed to the United Nations which have been made available for the use of WHO for specific health projects.

[6] Grants from the Public Health Service-National Institutes of Health for specific medical research projects.

[7] The Pan American Health Organization is also the regional office of the World Health Organization in the Western Hemisphere. These funds cover the activities of PAHO in that capacity.

COST PER PAPER ISSUED OF NIH INTRAMURAL PROGRAM

Mr. Laird. Dr. Shannon, I would like to discuss with you a minute the intramural program of the NIH. What is the cost per publication of each of the scientific papers, not including preliminary reports and abstracts, of your intramural program?

Dr. Shannon. I don't know, sir. I can get it for the purposes of the record.

Mr. Laird. The figure is available for universities and for private institutions. It has been used at various times. I would like to compare that figure with the figure of your intramural program. I would like that figure compared at this point in the record.

(The requested information follows:)

The average cost of preparing a paper for publication in the medical and scientific literature by a member of the staff of the National Institutes of Health during 1961 was $20,742.

ADMINISTRATION OF INTRAMURAL PROGRAM

Mr. Laird. It seems to me that the intramural program is becoming so large that it must present quite a few administrative problems. Is that true?

Dr. Shannon. Quite frankly, Mr. Laird, no, in that the intramural program isn't run as a monolithic structure. First, it is decentralized into a series of seven Institutes; and the Institutes in turn are decentralized into a series of laboratories, with varying degrees of autonomy.

I would compare the complexities of their administration as being comparable to the administrative complexities of conducting research at Harvard or research at the University of California, in that different levels have different types and different degrees of responsibility for precisely what is done.

The problems that come to my attention and to Dr. Mider are primarily matters that relate to personnel, to services, and to the housekeeping activities.

The problems of so-called scientific direction or scientific leadership are no more complicated, no more complex, in a large scientific organization within the Government than they are in a large scientific organization outside the Government.

Mr. Laird. This decentralization that you speak of, Dr. Shannon: Doesn't this do away with a lot of the benefits that can be gained from close communication between investigators?

Dr. Shannon. I don't think so at all, Mr. Laird. Let's take decentralization by layer. In the first place, Dr. Mider is responsible for the conduct of our direct operation. He in turn looks to associate directors in charge of research in each of the institutes for very broad program development so that the broad programs are fittingly suited to the objectives of the institute concerned. The interaction between laboratories with interests related but in different institutes is in no way hindered or hampered.

It is actually facilitated by this type of decentralized administration. For example, in the area of viral diseases, we have a broad interplay at the present time extending from basic virology in the Allergy and Infectious Diseases Institute, extending through the Cancer Institute, involving the Institute of Neurological Diseases and Blindness, and also including the Heart Institute.

The interplay of these scientists is responsible in no small measure for the very rapid advances in certain aspects of virology on our campus. Some of those advances, I believe, could not have taken place elsewhere.

The virtue of the admittedly large and complex organization such as ours is that it permits—provided it has a suitable administrative structure—the regrouping of different laboratory groups as long-term objectives change with changing times.

I would say administrative complexities from the standpoint of housekeeping, yes; administrative complexities from the standpoint of the substance of science, no.

RESEARCH BY INDIVIDUAL PRACTITIONERS

Mr. LAIRD. I have written you on several occasions during the past few years about trying to encourage individual practitioners to take part in the medical research program of the National Institutes of Health. I wrote you one letter several pages long in which I went into the benefits I thought could be gained by getting actual practicing physicians to take part actively in this program.

How many grants are made to individual practicing physicians; or individual investigators connected with clinics or hospitals that are not connected with universities and colleges? Would you have that figure?

Dr. SHANNON. First, I may say there are a great many. Secondly, I can furnish that figure for the record because our grants are broken down by type of institutions. This can be pulled together quite easily.

I would like, though, to have some clarification. For example, would you consider the Michael Reese Hospital in Chicago as one? Or would you consider the Mayo Clinic in Minnesota as another?

Mr. LAIRD. Yes. The Cleveland Clinic isn't tied in directly with a medical school, is it?

Dr. TERRY. That is right; you are correct.

Mr. LAIRD. Those institutions along that line. They, of course, are the larger ones. But that is the kind of thing I was interested in.

Dr. SHANNON. There is one thing that will make this compilation a bit hard, and I want to explain the difficulties now rather than write about it at great length when the listing is submitted.

There has been a trend, in the last 10 years, for many of these clinics, whether be they small or large, to develop fairly close associations with university groups. I point out that the Mayo Clinic has developed such an association with the University of Minnesota in the last 5 or 6 years. Also the Anderson Clinic in Texas is loosely associated with Baylor. Nevertheless, I would consider these two institutions as being predominantly the types of clinic that you have in mind, where the primary purpose of the clinic is the care of patients, but where, in order to provide a combination of suitable care for patients and suitable training, they have added or have expanded research activities.

We will identify where we know that the clinic has such an association; but we will not include in this listing any institution that might be considered almost a part of an academic institution.

For instance, I would not put Massachusetts General Hospital in such a listing because, while it is a wholly independent institution, it really represents part of the departmental structure of Harvard University, the departments being medicine, surgery, pediatrics, and so forth.

(The requested information follows:)

TABLE I.—*NIH research project grants to nonacademic*[1] *institutions, fiscal year 1961*

Types of institutions:	*Number of project grants*
1. Hospital, medical centers, clinics, dispensaries, homes, and associated research institutes and foundations	1,327
2. Research institutes, laboratories, operating foundations, centers[2]	541
3. Federal, quasi-Federal, State county, city boards, and similar agencies	340
4. Voluntary associations, councils, boards, bureaus, societies, guilds, commissions, congresses; and centers, clinics, institutes not dealing with the sick	226
5. Commercial agencies solely or partly engaged in research	107
6. Other miscellaneous agencies	2
7. Private individuals	33
Total project grants	2,576

[1] Hospitals or clinics identifiable by name as under university or medical school administration have been excluded from the count.

[2] Including 2 museums and 1 zoo.

TABLE II.—*Sample of 536 research grants to nonacademic hospitals and related institutions, fiscal year 1961*

Research grants	Number of grants	Percent of sample
1. Grants with M.D.'s as principal investigators or coinvestigators	324	60
2. Grants with M.D.'s on the project but not as principal investigators or coinvestigators	51	10
3. Total number of grants in which M.D.'s participated in the research	375	70
4. Number of grants in which 1 or more M.D.'s had, independently, some academic connection (although the grant did not)	36	7

NOTE.—Total number of persons identified as M.D.'s who participated in the research under the 536 grants equals 574, with reasonable assurance that there were other M.D.'s among 78 persons whose professional degree was not stated.

AFTERNOON SESSION

Mr. FOGARTY. The committee will come to order.

Mr. Laird was questioning.

PAY LEVEL OF NIH SCIENTISTS

Mr. LAIRD. Dr. Shannon, it has been frequently stated that the level of pay of personnel at the National Institutes of Health in the scientific research area is lower than comparable positions elsewhere. Now, is this comparison based on comparisons with industry or comparisons in the academic area?

Dr. SHANNON. Comparisons in the academic area, Mr. Laird. For instance——

Mr. LAIRD. I note there was a study made by the Association of American Universities which shows that the average rate of pay in a university for assistant professors is in the range of $7,000 to $9,000; for associate professors from $8,000 to $10,000; and for full professors from $10,000 to $17,000.

These figures were quoted on a 12-month basis.

I am sure that there are some of the top positions in the universities and colleges that are in a higher salary bracket than this, but this was the average range that they spoke of in their study. How do the salaries compare at the National Institutes for people with jobs comparable to assistant professor, associate professor, and full professor?

PROBLEMS OF SALARY COMPARISONS

Dr. SHANNON. Mr. Laird, in the first place, it is impossible to compare our salary structure with the salary structure you noted because this study includes the humanities, the arts, as well as the sciences. In any large compilation of statistics, it will show that salaries for academic people in the arts are considerably less than academic people in science and technology. That is the first thing.

In the second place, when one compares one institution with another institution, one has to take roughly comparable institutions in terms of the mission that they are undertaking. We can only compare our salaries with institutions that have comparably broad and well-supported research activities. For example, some of our medical schools have almost no research activities, others have a very large program, roughly the size of any one of our larger Institutes.

Where one finds technically qualified people whose employment is not for purposes of research but purely for purposes of instruction, the salary level will be quite low as compared with a qualified research institution.

COMPARISON WITH SELECTED INSTITUTIONS

If one wants to compare the NIH with comparable institutions in terms of the magnitude and significance of the research activity, then one must make a comparison between NIH and Harvard, Michigan, Wisconsin, MIT, and institutions of that sort.

Here we can give you very precise figures. We have just recently collected those comparisons for former Secretary Folsom, who is a person——

Mr. LAIRD. Can you supply those for the record?

Dr. SHANNON. That is what I was going to suggest, that we might supply these.

It will have greater usefulness if we identify the schools but we should prefer not to identify the salary structure of each school. In other words, we can give you the particular schools we surveyed and give you the results of the survey without tying a specific school to a specific salary schedule.

Mr. LAIRD. Is there some objection to that?

Dr. SHANNON. Not to the point where the school would object, but in giving us the data——

Mr. LAIRD. If you take a school like the University of Wisconsin, that is a matter of public record. It is a State-supported school.

Dr. SHANNON. Well, the one I have particularly in mind, from which we got the first figures, is the University of Chicago. Dr. Stanley Bennett is the new dean. He said that if we had to use them tied to the University of Chicago, that would be all right, but if we had to use them in a public document, he would prefer we did not identify them with Chicago.

Mr. LAIRD. Well, I think we could gain something if you gave us the group and weighted it out.

Dr. SHANNON. The schools that we have in this most recent survey are Harvard—do you know about Chicago?

Dr. PRICE. Yes.

Mr. LAIRD. The University of Chicago?

Dr. SHANNON. The University of Chicago. I cannot remember. We did this a year ago. We had five schools.

Mr. LAIRD. How did you pick the five schools?

Dr. SHANNON. We picked several State schools and several private schools that had very well-elaborated programs in the life sciences.

And I might say, sir, we also picked them also on the basis of personal acquaintanceship. So that we could talk to them informally and not have to make an official request for information.

Mr. LAIRD. Well, do you feel that the schools are having a tougher time maintaining their faculties than you are in maintaining your personnel?

COMPARISON WITH TOP UNIVERSITY RESEARCH SALARIES

Dr. SHANNON. Let me pass that for the moment and present a point I did not make. Let me compare the situation in the schools with that at NIH in terms of dollars so we can have a better frame of reference.

Our top salary is $19,000. In a comparable situation in the schools I have in mind, the top salaries are on the order of $30,000; so we are talking about substantial differences between many of our academic institutions and the National Institutes of Health.

Mr. LAIRD. Of course, in those schools you go from $30,000 down quite fast.

Dr. SHANNON. Mr. Laird, surprisingly enough, this is no longer the case. At the present time, the most difficult job the schools have is to obtain an acceptance for the chairmanship of a department as opposed to a separate full professorship. The salary differential between the full professor and the chairman of the department is not very great. Yet, the administrative responsibilities are tremendously different. One of the greatest difficulties our universities and schools are having at the present time is the maintenance of really topflight people in positions of broad administrative responsibility.

They are not having difficulty in holding those individuals who have primarily a professional research responsibility and who have an opportunity to do such teaching as they wish to do.

Given this freedom, the academic position now has a very high degree of stability. There is relatively little loss of the top people to industry. We are building up in our better institutions very stable faculties of very high caliber.

I might say, also, that this is in no small measure due to the programs available through the National Institutes of Health as a result of considerations which this committee has given the problem over the years.

We are arriving at a position of being able to stabilize the medical sciences in a very satisfactory way. I can look forward to the time, say in 3 or 4 years, when, as the result of the progress of our programs, we shall have returned to a situation as stable as that which obtained in the twenties when schools of higher quality were supported primarily from resources of their own—foundations, endowments, things of this sort. This is developing very well.

Mr. LAIRD. Well, I think it should be interesting to have this comparison for the record that we discussed earlier.

Dr. SHANNON. This we shall do.

(The requested information follows:)

RECENT STUDIES AND REPORTS SUPPORTING INCREASED SALARIES FOR TOP SCIENTIFIC JOBS

1. *Recent exchange of information between NIH and five leading medical schools*

The NIH is in direct competition for quality scientists with university medical schools, especially those with well-defined research activities. A survey of five such universities shows:

University A pays a department chairman in the basic sciences a top salary of $24,000. A clinical department chairman receives a top salary of $27,500, and the university is prepared to offer $30,000 in the next academic year.

University B pays executive professors in clinical departments from $16,000 to $32,000; the overwhelming majority of executive professors receive in excess of $26,000. Full professors in clinical departments receive from $15,000 to $30,000, and the majority of these men are at the upper end of the pay range.

University C pays 13 preclinical professors an average salary of $21,000, and its dean $30,000.

University D pays department heads in the school of public health from $18,575 to $29,700. The top salary for a full professor in the medical School is $30,000, with an average of $21,325.

University E pays a professor and chairman of a clinical department between $20,500 and $32,000. Professors receive between $18,800 and $26,000.

2. *Salaries of deans and professors in medically related professional and graduate colleges (clinical medicine 1960–61) (app. 1)*

The Office of Education, DHEW, makes an annual survey of college salaries for use in their publication "Higher Education Planning and Management Data." An analysis was made of the raw data used in the compilation of table 21B, "Average 11–12-month salaries of deans and faculty in medically related professional and graduate colleges" of the 1960–61 report. A total of 60 schools reported salaries for deans; a total of 79 deans were employed by the schools. The raw data revealed that 36 of these 60 schools pay their deans an average salary higher than the NIH maximum of $19,000; 42 of the 60 schools reported that at least one dean was earning more than the NIH ceiling. The maximum salary reported for an individual dean was $32,000. These salaries do not include additional emoluments in the form of publication royalties and consultancy fees not available to the Government scientists, nor do they include some of the fringe benefits—such as lowered college tuition for dependents—peculiar to educational institutions. The same data revealed that the school which pays its dean $30,250 employs 18 professors of clinical medicine at an average salary of $30,000. At least one of these professors is paid $37,000 per year.

3. *Report of 1961 salaries paid by 27 medically related research institutions—confidential survey made in 1961 by one member of the group (app. 2)*

This survey includes medical schools and other medical research centers in direct competition with the NIH. It compares salaries for positions which equate to the professorial level. In both the 1960 and 1961 surveys, almost all of the participating institutions reported salaries in excess of the $19,000 maximum at the NIH. In the 1961 survey, the NIH position compared to the survey total, as follows:

	Range of actual salaries [1]		Medians,[2] all
	NIH	All	
Member (low)	$13,730	$5,300	$12,000
Professor (high)	19,000	40,000	23,000
Associate member (low)	10,635	2,500	10,000
Associate professor (high)	13,770	27,000	17,200

[1] All salary data as of October 1961.

[2] Medians of all lowest and highest salaries reported by the participating institutions.

In evaluating the above data, it is important to remember that other participants exclude those positions which normally would be above the Laboratory Chief level at the NIH.

4. Salaries requested under research career award program

This program authorizes awards to full-time faculty members of professiorial rank or lower and provides for annual salaries paying up to $25,000. These salaries are required to be consistent with current university scales. Of 81 applications received before November 1961, many from faculty members below professorial rank, 40 were requests for stipends above $19,000 per annum.

APPENDIX 1

Average salaries for Deans and Professors in medically related professional and graduate colleges, 1960–61

AVERAGE SALARIES FOR DEANS

Number of deans (79):	*Average salary*
1	$30, 250
1	27, 500
1	27, 000
1	27, 000
1	27, 000
1	25, 452
1	25, 000
1	25, 000
1	25, 000
1	25, 000
1	25, 000
2	24, 662
3[1]	24, 000
1	23, 593
1	23, 500
1	22, 500
1	22, 500
1	22, 486
1	22, 450
1	22, 250
1	22, 000
1	21, 408
1	21, 000
1	21, 000
1	20, 500
2	20, 250
1	20, 004
1	20, 000
1	20, 000
1	20, 000
1	20, 000
1	20, 000
1	20, 000
2	19, 500
1	19, 425
1	19, 250
1	19, 000
1	19, 000
1	18, 750
2	18, 500
1	18, 500
1	18, 500
1	18, 000
1	18, 000
1	18, 000
3	17, 583
3	16, 667
3	16, 666
1	16, 500
2	16, 500
3	16, 300
1	15, 500
2	15, 600
1	15, 000
1	15, 000
1	14, 740
4	14, 700
1	14, 500
1	13, 900
1	10, 000

[1] Includes one maximum salary at $32,000.

AVERAGE SALARY FOR PROFESSORS

Number of professors (949)	Average salary
18	$30,000
15	27,025
26	24,292
27	23,442
9	23,145
17	22,794
6	22,150
4	22,120
2	21,500
17	21,015
44	21,000
21	20,565
6	20,000
18	19,744
13	19,251
13	18,761
17	18,750
15	18,490
11	18,318
20	18,202
2	17,900
8	17,488
17	17,249
15	17,160
13	16,980
66	16,926
20	16,805
9	16,667
14	16,598
21	16,557
23	16,543
14	16,443
18	16,362
5	15,900
3	15,867
16	15,749
13	15,676
13	15,673
20	15,500
10	15,120
7	14,670
16	14,507
5	14,480
2	14,000
21	13,952
19	13,863
7	13,728
13	13,577
18	13,375
29	13,272
6	12,750
70	12,746
4	12,500
43	12,372
9	11,556
8	11,152
24	10,333
8	10,000
1	8,500

Source: Raw data used in preparing table 21–B, U.S. Department of Health, Education, and Welfare. Office of Education; "Higher Education Planning and Manpower Data, 1960–61." Washington, D.C., U.S. Government Printing Office, 1961.

APPENDIX 2

1961—Comparison of salaries paid professional staff by 27 universities and institutes [1]

	Reported salary ranges [2]		Median ranges of lows and highs reported by institutions
	NIH	Survey	
Member (professor)	$13,730–$19,000	$5,300–$40,000	$12,000–$23,000
Associate member (associate professor)	10,635– 13,770	2,500– 27,000	10,000– 17,200
Associate (assistant professor)	8,955– 10,775	4,800– 22,752	7,500– 15,000
Research associate (instructor)	7,560– 9,380	3,000– 18,084	6,000– 10,500

[1] Excludes positions at other institutions which would be equated above the laboratory or branch chief level at NIH.

[2] All salary data as of Oct. 1, 1961.

1960 NSF STUDY OF SCIENCE SALARIES

Mr. LAIRD. Back in 1960, the National Science Foundation put out a study which I think you are familiar with.

Dr. SHANNON. Yes, sir.

Mr. LAIRD. And that particular study showed NIH in a very favorable position. Are you familiar with that?

Dr. SHANNON. Yes, sir. I do not think it showed it as favorable in the sense that we are better off than academic environments of comparable complexity and comparable net worth. I think it did show we were not as badly off as we are at the present time. We know where our competition is, in terms of the maintenance of qualified personnel, because we know the places to which our top people go to when they leave NIH; we know the salaries they move into.

Our experience is not based exclusively upon tabulations. It is based upon firm offers to individuals on our staff that have come to a sufficient number during the past 3 or 4 years, to give a very firm understanding of precisely what the competition is.

Mr. Laird. The colleges, I think, are finding that same competition, though.

Dr. Shannon. Well, sir, but they also find the money to meet it.

Mr. Laird. Has there been a change since the National Science Foundation made its survey?

Dr. Shannon. Did that not cover the years 1954 to 1957, Mr Murtaugh?

Mr . Murtaugh. I am not certain of the study Mr. Laird has reference to. There was a series of 1954 to 1957 studies.

Dr. Shannon. I think it was published in 1960 but I think it referred to earlier in the fifties.

Mr. Laird. Perhaps you cannot bring it up to date, but I would like to have that done if you can.

Dr. Shannon. We would not be able to bring that survey up to date, but we can give you current figures.

Dr. Terry. Mr. Laird, I have not heard all of the discussion and I do not know whether it has come into consideration or not, but I think very definitely the point should be brought into such a discussion of the relative importance of outside income which many, in fact, most, university people are allowed to accept, in contrast to the fact that we cannot accept any.

Mr. Laird. I think that is a fair point.

INTERCHANGE OF SCIENTIFIC PERSONNEL

Dr. Shannon. There is another point I would like to make, Mr. Laird. We feel we have a very solid responsibility to aid in the development of science. We do not feel that every scientist who is developed at NIH should stay at NIH.

We feel that a dynamic interchange of scientists between the Government and the university is consistent with developing of our national science efforts. Our problem is that we are losing people at too rapid a rate, and are unable to recruit comparable people in this interchange. So we have an outflow without a compensating inflow. This is basically bad because, if it is permitted to continue over too long a period of time, it will inevitably lead to mediocrity.

TRAVEL OF RESEARCHERS

Mr. Laird. Dr. Shannon, the grant program of NIH has been an unusually successful program which has enabled research in the health sciences in this country to surpass every nation in the world.

On several occasions it has been called to my attention that some of the grant-in-aid money has been spent for what you might term "excessive travel". How is this viewed by NIH?

Dr. Shannon. Well, basically, it is not subject to separate review before the fact but this is taken into account in the scientific review that is undertaken, project by project, before making the grant commitment.

We do not attempt, during the course of a grant to go into an academic environment and say that this man or that man is traveling too much.

Mr. Laird. You used to keep better check on that, did you not, back 3 or 4 years ago?

Dr. Shannon. No, sir. Until about——

Mr. Laird. I thought we used to get figures on that.

Mr. Kelly. I do not think so, Mr. Laird.

Dr. Shannon. No, sir.

Mr. Kelly. But we did have a policy some years ago, I am not sure how many years ago, under which an institution could only vary its budget by a relatively small percentage from its original plan without prior approval of the National Institutes of Health. And on reconsideration of that policy, it was modified so that the institution did not have to seek such approval for modifications of its plans.

Mr. Laird. Well, if a grantee takes your grant-in-aid money and says: "We will spend it on sending a group of people to Europe or to Africa or to South America", you can do that without having any approval from the National Institutes of Health?

Is that correct?

Dr. Shannon. Actually, yes, sir; it is correct.

I might say that we do not believe that it is done, because this would turn up in the audit review, which is conducted on an annual basis, as an abnormal distribution of expenditures by object. The individual who had taken such liberties with funds would suffer quite seriously in the review process.

GRANT FUNDS USED FOR FOREIGN TRAVEL

Mr. Laird. Well, then you would have the facts available on how much was spent on foreign travel from the grant money this past year?

Dr. Shannon. We would not have it easily available now, no, sir; not at this time.

Mr. Laird. What is the last year you have it available for?

Dr. Shannon. I do not believe we have it summarized as such.

Do you know, Mr. Murtaugh?

Mr. Murtaugh. We do have a breakdown on the use of funds by object and I think the latest year is 1960.

Mr. Laird. Let us have the figure on this area of travel for 1960, and then put in the figure for 1955. Because I do not believe this policy was in effect in 1955.

I think there has been a change since then.

Dr. Shannon. There is in this particular regard. Initially, when our grant program started, no funds were allowed for international travel. If an individual investigator wished to travel, he would make a separate application to the council for such funds.

Mr. Laird. But it seems to me that you have a different policy. We used to see it set forth in the justifications.

Dr. SHANNON. The international travel that you have referred to related to the direct operation.

Mr. LAIRD. I am not talking about the direct operation. I am perhaps confusing you on this. I am talking about the grant money.

Dr. SHANNON. In the grant money, to my recollection, Mr. Laird, we never broke out into international travel as a separate item for your consideration.

Mr. LAIRD. But I think you had to have separate approval for it.

Dr. SHANNON. We did up to about 1954 or 1955.

Mr. LAIRD. I think you will be surprised when you look at the 1955 figure and compare it with the 1960 figures.

Dr. SHANNON. I am sure it is much larger.

Mr. KELLY. I would just like to caution you, Mr. Laird, that in getting those figures, that no matter what the object class breakdown, or no matter what the purpose was, if you compared 1954 or 1955 and 1960 expenditures, that they would show a surprising increase.

It seems to me that you have to compare them as to what proportion of the total they are. Because during this period the National Institutes of Health has had a tremendous growth.

Mr. LAIRD. I just want to make myself clear on this point. It seems to me that the policy of discontinuing the requirement for approval has encouraged this travel tremendously. I cannot get at the figures from going over the justifications.

Dr. SHANNON. No, sir; they are not shown clearly.

Mr. LAIRD. I would like to find out what those figures are. I have serious questions about this idea of just having complete blanket authority on this without any prior review by the administrative agency in charge of it.

(The requested information follows:)

FOREIGN TRAVEL SUPPORTED FROM PHS RESEARCH PROJECT GRANTS

Until 1950 Public Health Service policy permitted the use of research project grants for any travel incidental to the successful prosecution of the research being supported. In 1950 the policy was changed to proscribe the use of research project funds for any foreign travel to international meetings.

In 1955 the policy was liberalized to permit professional staff of grant supported research projects to travel to international meetings where specifically recommended for approval by a national advisory council. The experience of the councils during the next 4 years brought firm conviction that the appropriateness of such travel should be evaluated by the officials of the grantee institution rather than by anyone at the national level. In 1959, therefore, the eight national advisory councils made unanimous recommendation that the grantee institution should determine for all travel proposed, domestic or foreign, whether it was necessary to the successful prosecution of the research project. While PHS approval was not required thereafter, PHS officials were obligated to note any undue increase in use of funds for travel.

To determine the end effect of these policy changes on the use of research project grants for foreign travel, reports of expenditures were analyzed for all grantees who had PHS supported research projects in both fiscal year 1954, the year before the liberalization of policy, and fiscal year 1960, the year following the second change. Data are also presented for fiscal year 1958, the year immediately before the second policy change. It is most interesting to note that leaving the decision to the grantee institutions has not resulted in a significant change in the percentages of total expenditures that went for foreign travel.

Percent of total expenditures for foreign travel

Fiscal year 1954	0.10
Fiscal year 1958	.23
Fiscal year 1960	.21

TEMPERATURE REGULATION IN MAN AND ANIMALS

Mr. LAIRD. This morning we talked about a particular grant and the kind of publicity that comes about from some of the grants.

I have here a story that appeared in the press, entitled "Pentagon Seeking the Camel's Secret." It goes on into a story with the dateline Sydney, January 9:

> Four American scientists flew off to Simpson Desert in a remote region of central Australia today to find out how camels survive without water. Under a U.S. Defense Department project, the scientists will spend 2 months in the area studying about 10 camels. The Americans are from Yale and Duke Universities.
>
> The Defense Department was reported helping to establish a stud farm for the animals in the United States so the adaptability of animals to desert warfare could be studied.

This was an interesting little story that appeared in the paper and I, being a member of the Defense Appropriations Committee, thought it would be a good thing to check into, just to see what the Defense Department was doing in this area.

I find out from the Director of Defense Research and Engineering in the Department of Defense, and I quote:

> The DOD is not involved in this project in question.

It goes on and tells that this is the National Institutes of Health. The National Institutes of Health grant is No. B-3826, entitled "Temperature Regulation in Man and Animals."

> Additional information about this investigation may be obtained from Miss Sylvia Kessinger, of the National Institute of Neurological Diseases and Blindness, telephone code 179, extension 8434, and from Dr. Harve Carlson of the National Science Foundation, code 178, extension 286.

There have been a lot of books written on this. I got the books out of the Library of Congress and I find that there are some very fine books written on this particular subject. I have those books in my office and also the research papers on this particular subject. It amounts to quite a bit that has been done in this area. I would like an explanation put in at this point in the record, as long as the Defense Department has passed the buck over to NIH—although they seemed to be mentioned very prominently in the newspaper article. Tell us what this particular project is, because I think this is one that certainly will be discussed at some time, Mr. Chairman, during the budget process this year.

Dr. SHANNON. We will be glad to do that. I can imagine what it probably is, but I would rather not discuss it without firm factual support.

Mr. LAIRD. Yes.

Dr. SHANNON. I will say this, though, that the National Institutes of Health would not be interested in establishing a stud farm.

Mr. LAIRD. I will give you that article, and you can put it in.

(The requested information follows:)

NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS, RESEARCH GRANT B-3826

STUDIES OF BODY TEMPERATURE REGULATING MECHANISMS

The regulation of body temperature is one of the most important homeostatic mechanisms of warmblooded animals. In the human, prolonged body temperatures above 106° F. are incompatible with life. A change in body temperature is one of the prominent features of many infectious diseases. Recently, the use of lowered body temperature during anesthesia has proven a valuable aid to surgery. An exact knowledge of the temperature-regulating mechanism is essential to further refinement of this technique.

Newly developed techniques, especially those involving the use of microelectrodes in the brain, now make it possible for the first time to record the activity of nerve cells within the brain that are involved in the temperature regulating mechanisms. In addition, refinements of the methods for measuring heat exchange now make possible an exact correlation between the regulatory function being performed and the activity of the nervous system responsible.

There is some evidence that the hypothalamic area of the brain may be the part of the nervous system which controls body temperature. However, this has not been satisfactorily substantiated and needs further exploration. Also to be explained are the roles of the skin and deep thermal receptors in the regulation of body temperature, especially their relationships to the hypothalamic area of the brain. In an effort to answer these questions, the investigators are conducting studies in animals by studying the electrical activity of the individual nerve cells of the hypothalamic area of the brain. These are being studied in response to various localized and generalized experimental temperature changes, as well as the responses of the skin and deep thermal receptors to controlled temperature changes.

In these explorations the relationships of the measurements of responses to temperature changes in the brain tissue, the skin, rectum, and tympanic ear will be studied in relation to the three basic thermoregulatory outputs, metabolic rate, vasomotor state, and sweating or panting. Techniques for introducing controlled temperature changes will range from the insertion of stainless steel thermodes—through which warm or cool water is circulated over the hypothalamic tissue (localized), to introduction of fever-producing toxic substances, as well as changes in the external temperature (generalized.)

As a part of this broad study of body temperature regulation, the camel will be used as an important experimental animal. The laboratory techniques used in other animals will be combined with field techniques for study of the camel in its natural environment. The elucidation of the highly developed means whereby the camel, living in the desert under conditions of hydration and water deprivation over long periods, is able to maintain its water and heat balance may be very helpful in furthering our understanding of the analogous temperature-regulating mechanisms in man.

JOINT NIH DEFENSE DEPARTMENT STUDIES

Dr. SHANNON. There are a number of projects that are of mutual interest to us and the Department of Defense, which involve the utilization of special equipment or specialized resources. It is not unusual for the Department of Defense to offer services to make it possible for a study to go forward.

I would say that this is very good, because it facilitates doing the work in the most effective way possible.

MISLEADING TITLES OF RESEARCH PROJECTS

Mr. LAIRD. Dr. Shannon, some of the titles of research grants, particularly in the behavioral sciences, are somewhat misleading. Do you care to comment on that?

Dr. SHANNON. Yes. The behavioral sciences are peculiarly susceptible to misinterpretation, because they deal with phenomena that are the common experience of everyone. They have to do with such factors as love, hate, and things of that general sort that the common man feels he already understands.

In point of fact, we are just approaching the time when we shall have an appreciation of the importance of certain of these factors in the emotional development of the child and for that matter the behavior of adults. It is quite apparent that many of the problems of childhood such as juvenile delinquency, drug addiction, and things of this sort, stems from the distortions of relationships.

We are convinced that very deep scientific exploration of these areas is essential if we are to find valid answers to some of our more important problems with emotionally disturbed children. I am equally convinced that when one uses models of behavior from the animal kingdom—maybe rats, mice, monkeys, guinea pigs and the like—and when these investigations find their way into the public print, they will appear under titles that are completely misunderstood and will be presented out of the context of the very important work they are underpinning.

I think it behooves us, as science administrators, to try to foster a broader public understanding of the relationship of these apparent everyday problems to the very serious investigation of disease, the serious investigation of mental disorders and emotional states, otherwise we are going to be increasingly misunderstood. We are at the point now where we have to delve quite deeply into the seat of emotions and the effect distortions of these emotions have on both the young and the old.

IMPORTANCE OF RESEARCH IN EMOTIONAL DISTURBANCES

I am wondering if it would not be worthwhile for you gentlemen, in discussing our programs on the floor of the Congress, to call attention, in a positive way, to the fact that there are very broad problems seated in disturbances of emotions, including juvenile delinquency and the like that must be investigated in model systems that involve animals, since it is not possible to conduct controlled studies with humans. Out of this we shall repeatedly have isolated results that are going to be misinterpreted in the press, and unless understood by the Congress, will be subject to ridicule.

This is a very important activity in which the NIH is very deeply involved. We have discussed the possibility, precipitated by the episode we were talking of this morning, of trying to involve the television industry in promoting public awareness of the type of basic research that is required to solve some of these problems.

Mr. FOGARTY. You are going to give us some specific examples of what has been accomplished in some of these areas?

Dr. SHANNON. What we thought we would do is to take this project of Dr. Harlowe as an example.

These cases are going to come up, in increasing numbers and I think we should have a positive approach to that, rather than just countering each unjustified attack that comes down the pike.

Mr. FOGARTY. Give us some examples.

Dr. SHANNON. Yes, sir.

(The requested information follows:)

Looming large among our current unsolved and pressing health problems are those related to the aging of our population and to human relations and human behavior. Among these are juvenile delinquency, drug addiction, alcoholism, and mental illness which, despite vast advances in treatment, still fill half the hospital beds of the country. Consequently, we may expect research in the medical and health fields in this and the next few decades to be directed increasingly to study of behavioral and social problems.

The methods of biomedical research are essentially the same, regardless of the particular problem under study. Among the methods which have brought us many of the achievements of the past is the use of an experimental model. The model is constructed to reproduce as closely as possible what is known or believed about the particular subject under study. It is then manipulated, things put in or taken away, or its components rearranged, and the results observed. From such study comes knowledge which could not be obtained from studying a particular disease or health problem in man because man could not be manipulated as the model can be.

The model may consist of bacteria; a bacteria model, for example, was used in studies leading to one of the most significant recent research achievements, the partial "cracking" of the genetic code. The model may consist of laboratory animals, from mice to monkeys, or of mathematical symbols and combinations, such as are used with the large computers.

The models and other methods of biomedical research are usually not of great interest to the average man, though he may know about the Pavlov dog whose mouth always watered in conditioned reflex response to a bell which originally meant dinner. In the future, however, both the models and the subject of biomedical research will hold greater interest for the average layman, as the subjects, and the models for studying them, are increasingly concerned with more familiar matters, for example, human relations and emotions.

The mere fact of familiarity, however, does not constitute knowledge. Centuries ago the disease, malaria, was familiar to many. The cause was believed to be bad air. Today, as the result of biomedical research, the cause is known to be a parasite, or germ, and scientists know how the parasite spreads and how to prevent and cure the disease.

The scientific community is almost as much in the dark today with regard to knowledge of the behavioral disorders as it was centuries ago with regard to malaria. There are many theories on how to prevent juvenile delinquency, alcoholism, and marital discord and divorce. Yet the kind of precise knowledge needed to produce cures for these and other social ills is still lacking.

In the search for such knowledge, scientists need to study emotions, such as love, hate, and fear, and their effects both on the body and on the individual's relations with others. For some of these studies, close detailed observations of humans as they behave in family and other groups are needed. For other studies, models consisting of suitable nonhuman animals are needed.

Progress is being made, although in the behavioral as in any other field, scientific research advances slowly. There are not too many so-called happy accidents in science, such as the discovery of penicillin. The second major antibiotic, streptomycin, was discovered as a result of years of painstaking study of micro-organisms in the soil, their antagonisms, and the action of some groups on other groups which were the causes of human disease.

Among examples of advances in the behavioral sciences the following may be cited:

The effects on behavior of reserpine, widely used tranquilizer and antihypertensive drug, were found through studies with monkeys. Subsequent studies have shown that reserpine can interact with the body's nervous and hormonal mechanisms to produce a biochemical picture almost indistinguishable from the classical "stress" response evoked by prolonged exposure to cold, pain and similar unpleasant stimuli. Other studies have now resulted in a reserpine analog with the same effects as reserpine but with readily reversible action and only temporary and noncumulative effects.

From studies of pigeons and their pecking response has come the reinforcement theory of learning with such practical applications as the automatic teaching machines used successfully to facilitate instruction from kindergarten through college and in the Armed Forces; techniques for teaching basic reading and speaking skills to mentally retarded as well as normal children and to induce abnormally withdrawn children to be willing to perform to the full extent of their real capacity. Techniques used in studying the pigeon's pecking response are now being utilized in pure research and in industry. In the pharmaceutical industry they are being applied to drug screening at the preclinical level. The principle of reinforcement has been extended and developed into a comprehensive theory of behavior which has been applied to the human organism in the study of psychotic behavior and in analysis of verbal behavior as well as in design of teaching devices.

Greater knowledge of the physiological mechanisms affecting behavior and of the influences on behavior of body chemistry have come from studies of the common Norwegian rat, studies which also led to the widely successful block system of rat eradication based on the finding that rat behavior is such that they do not cross streets.

The role of the mother in preventing the negative effects of stress in the young, and the effects of environmental factors on the development of a neurosis were clarified in studies in which sheep and goats were subjected to carefully controlled stress situations. Understanding of the dynamics of child development and parent-child relationships, and the etiology of mental disorders has been aided by these studies. Later, when the effects of combat stress on American soldiers in Korea were studied, it was possible to draw parallels between the signs of approaching breakdown in soldiers and the abnormal behavior of the experimental animals.

The importance of stimulation and handling early in infancy for development of differential and emotional responsiveness to stress was shown in another study in which rats were used in the model system. Existence of critical periods in the development of the organism during which infantile stimulation has its greatest effect on reaction to stress was discovered. Exploring the effect in infantile experience on later behavior also showed that the nonstimulated rats displayed significantly greater emotionality in a novel situaiton than the stimulated rats.

While no timetable can be given for further advances in the behavioral or any other science, it can be expected that individual findings in the behavioral field will continue to gain more popular attention, because of the subjects dealt with, than individual findings have had in other fields. Studies of young married couples, of drug addicts, of juvenile delinquents, are bound to arouse more interest than biochemical studies of the catechol amines or biophysical studies of the permeability of membranes. Breakthroughs immediately applicable to human health are not expected from the latter kind of studies, nor will breakthroughs immediately applicable to humans come from the early and preliminary findings in behavioral studies.

CANCER TEACHING GRANTS

Mr. LAIRD. Dr. Shannon, for a number of years undergraduate cancer teaching grants for schools of medicine, osteopathy, and dentistry have been made available through NIH.

Dr. SHANNON. Yes, sir.

Mr. LAIRD. These grants have run about $25,000 annually for all schools of medicine and osteopathy and for a lesser amount to dental schools. And as I understand the purpose has not been for research training but for the teaching of medical students about cancer, for instance, subjects that must be included in every medical school curriculum, regardless of whether they obtain a grant or not.

Dr. SHANNON. Yes, sir.

Mr. LAIRD. I would like to raise the question as to whether these continued grants for this purpose are justified, since they are not in support of research or research training.

Dr. SHANNON. Well, in the first place, they are quite helpful. The authority under the Cancer Act—and also under the Heart Act and the Mental Health Act——

Mr. LAIRD. I did not question your legality.

Dr. SHANNON. No; I was getting back to how they started—includes the development of a general understanding, both among professionals and among laymen, of cancer in all its variations.

When these grants were first made, there was a complete lack of any attempt to coordinate cancer teaching throughout the 4 years or among the various departments. These grants were for purposes of developing a coordinated program pulling together information from the various departments and presenting it sequentially to the students. This has been very effective in heart, in cancer, and in mental health.

These funds have resulted in strengthening the operation of the schools by supporting, for example, the appointment of professors of oncology and the like.

So I think that this has to be viewed in the light of professional education in cancer rather than as a general educational subsidy to the school. And I would feel very——

Mr. LAIRD. Really, what it is is a general education subsidy right now?

Dr. SHANNON. No, sir. I think it is a professional subsidy that permits the pulling together instruction that relates to cancer for the systematic exposure of every student who goes through the complex medical school education.

Mr. LAIRD. Well, I would have thought that probably with the advent of the institutional grant, that this type of approach would be discarded by NIH.

Mr. KELLY. The institutional grant would not be available as a substitute for this. The institutional grant is available only for research and research training.

OTHER ACTIVITIES NOT DIRECTLY RELATED TO RESEARCH

But there is more than just this one item in the National Institutes of Health budget, which is not related to research or research training. We talked the other day about the appropriation structure and the method by which we have tried to accommodate it to the organization. But the exception is made in the National Institutes of Health because the Congress wanted to pull together the total mental health program and the total cancer program, and so forth. In addition to research and research training, there are significant funds that are included in the National Institutes of Health budget that relate to the training of personnel to engage in the service functions as distinguished from the research function in these areas, and including demonstrations and control activities that relate to these functions as distinguished from research and research training.

POSSIBILITY OF DISCONTINUING TRAINING GRANTS TO MEDICAL SCHOOLS

Mr. LAIRD. My only thought here was that there are other areas that are probably more in need of assistance in some of the medical schools than this particular area, because this is going to be done anyway.

Dr. SHANNON. Sir, it was not done before the program was started. It would be done now without these grants but it would not be done as effectively as it can be done with the support these grants provide.

I may say that the other Institutes, Neurological Disease and Blindness——

Mr. LAIRD. I realize the other Institutes, and I was using this as——

Dr. SHANNON. No, but they have asked to support comparable programs in their areas of interest.

Mr. LAIRD. Well, Heart is in this now. Does not Heart do this?

Dr. SHANNON. Cancer, Heart, and Mental Health.

Mr. LAIRD. Yes.

Dr. SHANNON. Several others want to do it also.

We have taken the position that we should like to hold the program to these three Institutes where it is more easily justified. We should like ultimately to drop it when some sort of general support for education is made available to the schools. This cannot be blanketed into any other program than one that is aimed at the general education function.

Mr. LAIRD. Well, really what you are doing here is supporting a teaching position.

Dr. SHANNON. Yes, sir.

Mr. LAIRD. In these medical schools.

Dr. SHANNON. That is correct.

Mr. LAIRD. And I think a lot of people do not realize that what we are doing here is direct aid for teachers' salaries, in the heart, cancer, and mental health area.

Dr. SHANNON. That is correct, sir.

Mr. LAIRD. And this is an out-and-out straight grant for teachers' salaries.

Dr. SHANNON. That is correct, sir.

Mr. LAIRD. I did not realize that it could not be covered on the institutional grant basis.

Dr. SHANNON. No, sir.

Mr. LAIRD. I am glad to have that clarified.

Mr. FOGARTY. This is one of the programs that has been universally supported by all professional groups, including the AMA.

Dr. SHANNON. That is correct.

Mr. FOGARTY. I have said this many times; this is a concrete example of Federal aid to medical education, in my opinion. I agree with you on that.

Mr. LAIRD. I was just raising some questions about it, because it looked that way to me; and I just wondered whether the necessity is still there.

Dr. SHANNON. Yes, sir; the necessity is still there.

I did not mean to take exception to your statement that it is Federal aid to the educational process. What I meant to say, if I did not, is that this is not equivalent to general aid—that is, the giving of unrestricted funds—because these funds are given to meet a deficiency in the heart field, in the cancer field——

Mr. FOGARTY. And the only Federal control is to see to it that it is spent for that particular purpose, that is all.

Dr. SHANNON. That is right.

Mr. LAIRD. That is the only control?

Dr. SHANNON. That is right.

We feel very confident that this is one of the very effective programs.

DEMOCRATIC PLATFORM ON MEDICAL RESEARCH

Mr. LAIRD. Dr. Shannon, the Democratic national platform stated with regard to medical research, and I quote:

> Expenditures for these purposes should be limited only by the availability of personnel and promising lines of research.

This is a sentence from the platform as it deals with medical research.

I have here before me a table of the Department of Health, Education, and Welfare appropriations and reserves for fiscal year 1962.

Mr. FOGARTY. May I say at that point that I agree 100 percent with what you have just quoted from the platform.

Mr. LAIRD. And I notice that under the National Institutes of Health, in administrative reserves, which are reserves imposed by the Secretary for forced savings, there is the amount of $44,577,000.

My question to you, Dr. Shannon, is, was personnel available and were promising lines of research available?

Dr. SHANNON. We believe they were, sir.

Mr. LAIRD. Then I refer further to the——

REPUBLICAN PLATFORM ON MEDICAL RESEARCH

Mr. FOGARTY. Did the Republicans not have anything on this in their platform?

Mr. LAIRD. Would you like me to put that in? I would be happy to put that in, also.

Mr. FOGARTY. I think we ought to keep this nonpartisan.

Mr. LAIRD. In response to the chairman, I would be very happy to put in the Republican platform in that area too. I appreciate this opportunity.

Under "Health" I will quote the applicable section:

> There has been a fivefold increase in Government-assisted medical research during the last 6 years. We pledge continued Federal support for a sound research program aimed at both the prevention and cure of disease, and intensified efforts to secure prompt and effective application of the results of research. This will include emphasis on mental illness.

Mr. FOGARTY. Well, I think that makes the point that if we are able to raise this budget by $100 million we will be in keeping with both platforms, and we can remind both Democrats and Republicans that they have an obligation to go along with us.

ADMINISTRATIVE RESERVES IN MEDICAL RESEARCH FUNDS

Mr. LAIRD. Well, I was really referring to the action of the Democratic administration in setting up these reserves, and trying to reconcile it with the Democratic platform, if that is possible.

Now, in further reference to these reserves, I would like to quote a couple more sentences of the Democratic national platform:

> Mental health patients fill more than half the hospital beds in the country today. We will provide greatly increased Federal support for psychiatric research and training and community mental health programs, to help bring back thousands of our hospitalized mentally ill to full and useful lives in the community.

Now, I look here under "Administrative reserves," and go down to the mental health activities. I find a reserve for forced savings was made in the amount of $5,234,000. A great portion of this reserve was in the area of training, is that not correct?

Dr. SHANNON. Training was $1.7 million and research $3 million.

Mr. FOGARTY. Mr. Laird, I have been using the expression, "Off-again, on-again programs," and I think it applies to this. I cannot understand why they cut back in 1962.

Mr. LAIRD. What I have always felt was that we should keep the progression of this program on a rather level keel. I understand the problems that the administration faces, but I wondered, in conjunction with these reserves in mental health, whether there were available personnel and promising lines of research to use this training money and research money.

Dr. SHANNON. Mr. Laird, we believe there were available personnel for the training funds. I think that we volunteered a small sum in the research area, the amount of which——

Mr. LAIRD. I was only referring to the forced savings.

Dr. SHANNON. I see.

Mr. LAIRD. I am talking about the $5,234,000.

Dr. SHANNON. Then we would say that personnel were available, sir, yes. At least, that was our belief.

Mr. LAIRD. That is all I have, Mr. Chairman.

DEPARTMENTAL BUDGET ALLOWANCES

Mr. FOGARTY. Doctor, your budget submission to the Department was $855 million.

Will you give the committee a breakdown of how that $855 million would be expended?

Dr. SHANNON. We shall be glad to.

Mr. FOGARTY. Then also, another table showing us how you could use $50 million more.

Dr. SHANNON. We should be glad to do that, sir.

Mr. FOGARTY. Those two.

Dr. SHANNON. Yes, sir.

(The requested information follows:)

DHEW 1963 Budget Proposal of $855 Million and Suggested Revisions

The DHEW 1963 appropriation request submitted to the Bureau of the Budget in October 1961, included $855 million for the eight operating appropriations of the National Institutes of Health. The manner in which this amount was distributed by activity is shown in the first column of the following table. This distribution was relevant to the information available at that time. However, subsequent operating experience and new information now available would modify earlier decisions for some activities. Therefore, a revised distribution, more appropriate to current information, is provided in the second column of the table for comparison.

[In thousands]

Activities	DHEW request	Revised projection	Adjustments
Grants and related contracts:			
Research:			
Regular program	$402,192	$409,433	+$7,241
General research support grants	30,000	30,000	
Scientific evaluation grants	1,333	1,333	
International centers for medical research and training	3,192	4,000	+808
Gorgas Memorial Laboratory	250	250	
Clinical research centers:			
General	33,500	33,500	
Categorical	30,000	16,400	−13,600
Special resource centers	7,500	7,500	
Primate centers	9,000	5,000	−4,000
Total, research	516,967	507,416	−9,551
Fellowships	31,080	31,580	+500
Training	136,000	145,920	+9,920
State-control programs	15,250	15,250	
Community demonstration projects	4,000	4,000	
Total, grants and related contracts	703,297	704,166	+869
Direct operations:			
Research	67,540	67,540	
Collaborative studies	49,500	47,700	−1,800
Biologic standards	3,369	4,000	+631
Training activities	921	1,221	+300
Professional and technical assistance	11,672	11,672	
Review and approval	14,603	14,603	
Administration	4,098	4,098	
Total, direct operations	151,703	150,834	−869
Total estimate	855,000	855,000	

The basic change in projected programing has been influenced by the recently completed study on "Manpower for Medical Research" which supports the need for a substantial expansion of the supply of highly skilled, professional level technicians and subprofessional supporting personnel to assist in increasingly complex, highly instrumented medical research activities. A discussion of the implications of this report and an explanation of the revised estimates for 1963 appears in a statement beginning on page 2760. In moving toward an expanded program for training research manpower, it is estimated that a total of $31,580,000 for fellowships and $145,920,000 for training grants could be used in 1963. This represents increases of $500,000 and $9,920,000, respectively, over the October 1961 proposal to the Bureau of the Budget. The increases over the allowance in the 1963 President's budget are $5,584,000 for fellowships and $26,170,000 for training grants.

The second significant change is a reduction in the proposed allowance for categorical clinical research centers. The establishment of clinical centers to meet categorical Institute needs is developing considerably slower than earlier expectations particularly in the cancer and heart programs. Consequently, it appears that the need for funds in 1963 will be reduced even below the level projected in the 1963 President's budget. The revised estimate of $16,400,000 is a decrease of $13,600,000 below the October 1961 proposal and $1 million below the 1963 President's budget.

Minor adjustments have been made in certain of the direct operations activities as a result of a revaluation of needs. The estimate for collaborative studies has been held to the level of the President's budget with the exception of a $1,260,000 increase for "Chemotherapy contracts." The estimate for "Biologics standards" has been increased $631,000 to bring the total in line with the President's budget allowance of $4 million. The estimate for direct training has been increased by $300,000 to take advantage of opportunities to assign research personnel to oversea installations for training in these unique environments. This program will expand the number of individuals with a broadened background resulting from oversea experience and will also serve as a resource for much-needed personnel to assist in carrying out U.S. commitments for research programs in these areas. These adjustments result in a decrease of $869,000 in the estimates for direct operations activities.

All balances resulting from adjustments in other activities have been added to the allowance for regular project grants, bringing this allowance to $409,433,000. This amount will support approximately 97 percent of the total anticipated approvals in 1963 totaling $421,923,000. The revised total is an increase of $7,241,000 over the October estimate and an increase of $32,369,000 over the President's budget allowance.

Use of an additional $50,000,000 over the 1963 President's budget

[In thousands]

	1963 President's budget	Additional $50,000,000	Total
Grants and related contracts:			
Research:			
Regular program	$377,064	+$11,038	$388,102
General research support grants	30,000		30,000
Scientific evaluation grants	1,333		1,333
International centers for medical research and training	3,192	+808	4,000
Gorgas Memorial Laboratory	250		250
Clinical research centers:			
General	33,500		33,500
Categorical	17,500	−1,100	16,400
Special resource centers	5,000	+2,500	7,500
Primate centers	4,000		4,000
Total, research	471,839	+13,246	485,085
Fellowships	25,996	+5,584	31,580
Training	119,750	+26,170	145,920
State-control programs	15,250		15,250
Community demonstration projects	4,000		4,000
Total, grants and related contracts	636,835	+45,000	681,835
Direct operations:			
Research	65,400	+2,140	67,540
Collaborative studies	46,440	+1,260	47,700
Biologic standards	4,000		4,000
Training activities	832	+389	1,221
Professional and technical assistance	10,369	+500	10,869
Review and approval	12,639	+498	13,137
Administration	3,885	+213	4,098
Total, direct operations	143,565	+5,000	148,565
Total estimate	780,400	+50,000	830,400

Mr. FOGARTY. And if we can get both Democrats and Republicans to live up to their platforms, maybe we can get some action in this area and correct what has been done in 1962.

Mr. Denton?

Mr. DENTON. No questions. I think about everything has been covered.

Mr. FOGARTY. Do you have anything else you want to say, Doctor?

Dr. SHANNON. Mr. Fogarty, you have not discussed the Division of Biologic Standards. I would point out that there is nothing controversial there.

Mr. **Fogarty**. I thought it was in General Research and Services.

Dr. **Shannon**. Well, General Research and Services does encompass that, but——

Mr. **Fogarty**. I was going to get into it when we take up the appropriation item.

Dr. **Shannon**. I see; yes, sir.

Mr. **Fogarty**. You are going to be around, are you not?

Dr. **Shannon**. Yes, sir.

Mr. **Fogarty**. Thank you very much, Dr. Shannon.

HISTORY OF CONGRESSIONAL ACTION ON APPROPRIATIONS FOR NIH

We shall place the usual historical tables relating to the NIH appropriations in the record at this point.

(The tables referred to follow:)

HISTORY OF CONGRESSIONAL ACTION ON BUDGET REQUESTS FOR NIH

Year	Budget request			Appropriation		
	Obligational cash	Liquidating cash	Contract authority	Obligational cash	Liquidating cash	Contract authority
1932	$48,000			$48,000		
1933	48,000			48,000		
1934	54,775			54,775		
1935	50,000			50,000		
1936	64,000			64,000		
1937	64,000			64,000		
1938	464,000			464,000		
1939	515,000			515,000		
1940	587,750			707,000		
1941	712,120			711,000		
1942	705,000			700,000		
1943	1,278,270			1,278,270		
1944	1,291,000			2,555,020		
1945	2,835,000			2,835,000		
1946	2,078,000			3,414,700		
1947	10,799,500			[1] 8,125,448		
1948	22,403,000			28,876,000		
1949	45,701,460		$2,300,000	37,668,000		$10,300,000
1950	40,567,000	$3,900,000	3,595,000	50,167,000	[2] $4,925,000	15,425,000
1951	49,845,000	12,725,000		[3] 47,334,750	12,725,000	
1952	53,386,000	5,648,000		52,477,291	5,198,000	
1953	55,005,000			59,030,750		
1954	56,340,000			71,153,000		
1955 [4]	71,128,000			81,268,000		
1956 [5] [6]	90,023,000			98,458,000		
1957 [5]	[7] 126,725,000			183,007,000		
1958	190,183,000			211,183,000		
1959	211,814,000			294,383,000		
1960	294,279,000			400,000,000		
1961	400,000,000			[8] 560,000,000		
1962	583,000,000			[9] 738,335,000		
1963	780,400,000					

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[1] Includes $386,500 transfers.

[2] Not less than $3 million was earmarked for liquidating cash; an additional $1,175,000 was used for that purpose.

[3] Excludes $3,216,250 rescinded.

[4] Excludes $131,000 for Gorgas Memorial Laboratory.

[5] Excludes $147,000 for Gorgas Memorial Laboratory.

[6] Includes $90,000 transfer.

[7] Includes $200,000 transfer from other appropriations.

[8] Includes $12,139,000 for construction of mental health-neurology research facility.

[9] Includes $1 million for planning for a gerontological research facility; and $750,000 for modernization at the Rocky Mountain Laboratory, Hamilton, Mont.

Note.—Not all amounts in this table are comparable from year to year because of inconsistencies in the content of the appropriations. Prior to 1938 they exclude all salaries. Prior to 1943 they exclude all salaries other than those of employees of the National Cancer Institute. Prior to 1949 they exclude pay of regular corps officers. For 1948, 1949, and 1950 they include funds for support of narcotic hospitals at Fort Worth and Lexington which were subsequently transferred.

APPROPRIATION HISTORY, NATIONAL INSTITUTES OF HEALTH

Appropriation title	1938	1939	1940	1941	1942	1943	1944	1945	1946
General research and services, National Institutes of Health:[1] Obligational cash	$64,000	$64,000	$137,000	$141,000	$135,000	$743,400	$2,025,020	$2,274,000	$2,866,000
Salaries, expenses, and grants, National Cancer Institute: Obligational cash	400,000	400,000	570,000	570,000	565,000	534,870	530,000	561,000	548,700
Total, obligational cash	464,000	464,000	707,000	711,000	700,000	1,278,270	2,555,020	2,835,000	3,414,700

[1] Appropriation title changed from "Operating expenses" in 1958.

Appropriation title	1947	1948	1949	1950	1951	1952	1953	1954
General research and services, National Institutes of Health:[1]								
Obligational cash	$6,254,548	$10,126,000	$14,540,000	$12,075,000	$14,313,900	$15,756,500	$16,598,750	$4,675,000
Contract authority				1,925,000				
Salaries, expenses, and grants, National Cancer Institute:								
Obligational cash	1,820,900	14,500,000	14,000,000	14,725,000	15,086,000	15,031,750	17,887,000	20,237,000
Liquidation cash				4,175,000	5,000,000	4,625,000		
Contract authority			8,000,000	6,000,000				
Mental health activities:								
Obligational cash		[2] 4,250,000	[2] 9,128,000	[2] 10,862,000	7,130,000	9,988,737	10,895,000	12,095,000
Liquidation cash				750,000	2,375,000	573,000		
Contract authority			2,300,000	2,150,000				
Salaries, expenses, and grants, National Heart Institute:								
Obligational cash				10,725,000	8,850,000	10,082,650	12,000,000	15,168,000
Liquidation cash					5,350,000			
Contract authority				5,350,000				
Dental health activities: Obligational cash				1,780,000	1,954,850	1,617,654	1,650,000	1,740,000
Arthritis and metabolic disease activities: Obligational cash								7,000,000
Allergy and infectious disease activities: Obligational cash								5,738,000
Neurology and blindness activities: Obligational cash								4,500,000
Total:								
Obligational cash	8,075,448	28,876,000	37,668,000	50,167,000	47,334,750	52,477,291	59,030,750	71,153,000
Liquidation cash				4,925,000	12,725,000	5,198,000		
Contract authority			10,300,000	15,425,000				

[1] The "General research and services" appropriation provided unidentifiable amounts in the initial years of the "Arthritis and metabolic disease activities," "Allergy and infectious disease activities," "Neurology and blindness activities," and the National Heart Institute.

[2] Includes funds for support of narcotic hospitals at Lexington and Fort Worth which were subsequently transferred.

Appropriation title	1955	1956	1957	1958	1959	1960	1961	1962	Estimate, 1963
General research and services, National Institutes of Health: Obligational cash	$4, 675, 000	$5, 929, 000	$12, 122, 000	$14, 026, 000	$28, 974, 000	$45, 994, 000	$83, 900, 000	$127, 637, 000	$147, 826, 000
National Cancer Institute: Obligational cash	21, 737, 000	24, 978, 000	48, 432, 000	56, 402, 000	75, 268, 000	91, 257, 000	111, 000, 000	142, 836, 000	139, 109, 000
Mental health activities: Obligational cash	14, 147, 500	18, 001, 000	35, 197, 000	39, 217, 000	52, 419, 000	68, 090, 000	100, 900, 000	108, 876, 000	126, 899, 000
National Heart Institute: Obligational cash	16, 668, 000	18, 898, 000	33, 396, 000	35, 936, 000	45, 613, 000	62, 237, 000	86, 900, 000	132, 912, 000	126, 898, 000
National Institute of Dental Research: Obligational cash	1, 990, 000	2, 176, 000	6, 026, 000	6, 430, 000	7, 420, 000	10, 019, 000	15, 500, 000	17, 340, 000	17, 199, 000
Arthritis and metabolic disease activities: Obligational cash	8, 270, 000	10, 840, 000	15, 885, 000	20, 385, 000	31, 215, 000	46, 862, 000	61, 200, 000	81, 831, 000	91, 921, 000
Allergy and infectious disease activities: Obligational cash	6, 180, 000	7, 775, 000	13, 299, 000	17, 400, 000	24, 071, 000	34, 054, 000	44, 000, 000	56, 091, 000	59, 342, 000
Neurology and blindness activities: Obligational cash	7, 600, 500	9, 861, 000	18, 650, 000	21, 387, 000	29, 403, 000	41, 487, 000	56, 600, 000	70, 812, 000	71, 206, 000
Total, obligational cash	81, 268, 000	98, 458, 000	183, 007, 000	211, 183, 000	294, 383, 000	400, 000, 000	[1] 560, 000, 000	[2] 738, 335, 000	780, 400, 000

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[1] Includes funds for construction of mental health-neurology research facility.

[2] Includes funds for plans and specifications for a gerontological research facility; and renovations and alterations, modernization, and planning and construction at the Rocky Mountain Laboratory, Hamilton, Mont.

BREAKDOWN OF 1963 BUDGET BY ACTIVITY

Mr. FOGARTY. We will also place in the record the usual breakdown by activity of the President's budget.

(The breakdown follows:)

1963 President's budget

Obligations by activity	Management fund	GRS-NIH	Cancer	Mental	Heart	Dental	Arthritis	Allergy	Neurology	Total
Grants and related contracts:										
Research		$100,409,000	$65,830,000	$54,437,000	$89,720,000	$9,123,000	$68,754,000	$37,145,000	$46,421,000	$471,839,000
Fellowships		10,997,000	3,100,000	2,892,000	3,615,000	882,000	1,177,000	1,610,000	1,723,000	25,996,000
Training		29,400,000	7,780,000	44,650,000	10,539,000	3,741,000	9,525,000	5,350,000	8,765,000	119,750,000
State control programs			3,500,000	6,750,000	5,000,000					15,250,000
Community demonstration projects			4,000,000							4,000,000
Total grants and related contracts		140,806,000	84,210,000	108,729,000	108,874,000	13,746,000	79,456,000	44,105,000	56,909,000	636,835,000
Direct operations:										
Research:										
Direct operating funds			8,405,000	5,641,000	5,543,000	2,073,000	6,205,000	6,551,000	2,996,000	37,414,000
Reimbursements:										
Research supporting services	[1] ($8,499,000)		2,272,000	1,180,000	1,153,000	352,000	1,430,000	1,166,000	946,000	8,499,000
Clinical supporting services	(12,133,000)		3,186,000	1,869,000	2,272,000	182,000	1,491,000	1,326,000	1,807,000	12,133,000
Administrative management	[2] (7,354,000)		2,175,000	1,085,000	1,017,000	251,000	1,047,000	962,000	817,000	7,354,000
Advances for nonformula items	(405,000)									
Cafeteria	(425,000)									
Total reimbursements	(28,816,000)		7,633,000	4,134,000	4,442,000	785,000	3,968,000	3,454,000	3,570,000	27,986,000
Total research	(28,816,000)		16,038,000	9,775,000	9,985,000	2,858,000	10,173,000	10,005,000	6,566,000	65,400,000
Collaborative studies			34,341,000	2,573,000	1,330,000		650,000	4,050,000	3,496,000	46,440,000
Biologics standards:										
Direct operating funds		3,442,000								3,442,000
Reimbursements	(558,000)	558,000								558,000
Total biologics standards	(558,000)	4,000,000								4,000,000
Training activities				596,000	186,000				50,000	832,000

See footnote at end of table.

1963 President's budget—Continued

Obligations by activity	Management fund	GRS-NIH	Cancer	Mental	Heart	Dental	Arthritis	Allergy	Neurology	Total
Direct operations—Continued										
Professional and technical assistance:										
NIH				$2, 122, 000					$2, 300, 000	$4, 422, 000
BSS			$1, 836, 000		$4, 111, 000					5, 947, 000
Total professional and technical assistance			1, 836, 000	2, 122, 000	4, 111, 000				2, 300, 000	10, 369, 000
Review and approval:										
Direct operating funds		$1, 228, 000	762, 000	1, 487, 000	993, 000	$269, 000	$600, 000	$415, 000	704, 000	6, 458, 000
Reimbursements	[3] ($6, 181, 000)	1, 151, 000	973, 000	926, 000	965, 000	155, 000	737, 000	479, 000	795, 000	6, 181, 000
Total review and approval	(6, 181, 000)	2, 379, 000	1, 735, 000	2, 413, 000	1, 958, 000	424, 000	1, 337, 000	894, 000	1, 499, 000	12, 639, 000
Administration:										
Direct operating funds		550, 000	449, 000	353, 000	220, 000	123, 000	150, 000	141, 000	256, 000	2, 242, 000
Reimbursements	(1, 643, 000)	91, 000	500, 000	338, 000	234, 000	48, 000	155, 000	147, 000	130, 000	1, 643, 000
Total administration	(1, 643, 000)	641, 000	949, 000	691, 000	454, 000	171, 000	305, 000	288, 000	386, 000	3, 885, 000
Cancer research facility			52, 000							52, 000
Heart gerontology building					380, 000					380, 000
Outside reimbursements	(613, 000)									
Total direct operations	(37, 811, 000)	7, 020, 000	54, 951, 000	18, 170, 000	18, 404, 000	3, 453, 000	12, 465, 000	15, 237, 000	14, 297, 000	143, 997, 000
Total obligations	(37, 811, 000)	147, 826, 000	139, 161, 000	126, 899, 000	127, 278, 000	17, 199, 000	91, 921, 000	59, 342, 000	71, 206, 000	780, 832, 000
Unobligated balance brought forward			−52, 000		−380, 000					−432, 000
1963 estimate	(37, 811, 000)	147, 826, 000	139, 109, 000	126, 899, 000	126, 898, 000	17, 199, 000	91, 921, 000	59, 342, 000	71, 206, 000	780, 400, 000

[1] Excludes $179,000 in outside reimbursements.

[2] Excludes $217,000 in outside reimbursements.

[3] Excludes $217,000 in outside reimbursements.

ANALYSIS OF FINANCING OF RESEARCH GRANT APPLICATIONS

Mr. **Fogarty**. I am sure that we will have reason to make many references to this table we asked you to prepare showing estimated financed and unfinanced research grants. We shall put it in the record at this point.

(The table follows:)

Analysis of research grants (exclusive of special programs)

1963 estimate	GRS-NIH	Cancer	Mental	Heart	Dental	Arthritis	Allergy	Neurology	Total
1. Continuations and supplementals (assuming 1962 reserves not released)	$36, 915, 000	$44, 697, 000	$33, 527, 000	$56, 865, 000	$5, 259, 000	$47, 297, 000	$28, 173, 000	$33, 789, 000	$286, 522, 000
2. Number	(1, 427)	(1, 858)	(1, 312)	(2, 544)	(292)	(2, 348)	(1, 577)	(1, 209)	(12, 567)
3. Carryover from 1962	2, 055, 000	5, 440, 266	202, 000	--------	--------	4, 718, 265	2, 228, 251	3, 351, 908	17, 995, 690
4. Number	(86)	(224)	(8)	--------	--------	(256)	(124)	(120)	(818)
5. New projects	13, 832, 000	2, 803, 734	15, 054, 000	14, 986, 000	3, 029, 000	10, 293, 735	2, 810, 749	4, 337, 092	67, 146, 310
6. Number	(529)	(120)	(590)	(676)	(168)	(489)	(159)	(152)	(2, 883)
7. Additional indirect costs	767, 000	769, 000	709, 000	1, 044, 000	120, 000	905, 000	483, 000	603, 000	5, 400, 000
8. Total possible projects (1963 budget)	53, 569, 000	53, 710, 000	49, 492, 000	72, 895, 000	8, 408, 000	63, 214, 000	33, 695, 000	42, 081, 000	377, 064, 000
9. Number	(2, 042)	(2, 202)	(1, 910)	(3, 220)	(460)	(3, 093)	(1, 860)	(1, 481)	(16, 268)
10. Estimated approved projects not financed	5, 830, 000	8, 123, 266	5, 557, 000	7, 827, 000	572, 000	11, 706, 265	4, 915, 455	6, 662, 908	51, 193, 894
11. Number	(222)	(333)	(214)	(446)	(31)	(573)	(271)	(234)	(2, 324)
12. Total estimated approved projects	59, 399, 000	61, 833, 266	55, 049, 000	80, 722, 000	8, 980, 000	74, 920, 265	38, 610, 455	48, 743, 908	428, 257, 894
13. Number	(2, 264)	(2, 535)	(2, 124)	(3, 666)	(491)	(3, 666)	(2, 131)	(1, 715)	(18, 592)

GENERAL RESEARCH AND SERVICES, NATIONAL INSTITUTES OF HEALTH

THURSDAY, FEBRUARY 8, 1962.

WITNESSES

DR. G. HALSEY HUNT, CHIEF, DIVISION OF GENERAL MEDICAL SCIENCES

DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DR. G. BURROUGHS MIDER, DIRECTOR OF LABORATORIES AND CLINICS

RICHARD L. SEGGEL, EXECUTIVE OFFICER

DR. LUTHER L. TERRY, SURGEON GENERAL

JAMES F. KELLY, DEPARTMENT BUDGET OFFICER

Object classification

[In thousands of dollars]

	1961 actual	1962 estimate	1963 estimate
11 Personnel compensation:			
Permanent positions	1,858	2,221	2,777
Positions other than permanent	35	45	45
Other personnel compensation	72	66	66
Total personnel compensation	1,965	2,332	2,888
12 Personnel benefits	187	232	276
21 Travel and transportation of persons	117	202	262
22 Transportation of things	16	18	18
23 Rent, communications, and utilities	56	54	75
24 Printing and reproduction	13	56	70
25 Other services	174	82	465
Payment to "National Institutes of Health management fund"	1,162	1,605	1,800
26 Supplies and materials	711	842	1,024
31 Equipment	119	87	142
41 Grants, subsidies, and contributions	71,438	118,630	140,806
Subtotal	75,958	124,140	147,826
Deduct quarters and subsistence charges	1		
Total obligations	75,957	124,140	147,826

Personnel summary

	1961 actual	1962 estimate	1963 estimate
Total number of permanent positions	343	398	486
Full-time equivalent of other positions	6	8	8
Average number of all employees	306	355	446
Number of employees at end of year	347	416	504
Average GS grade	6.4	6.8	7.1
Average GS salary	$5,866	$6,071	$6,237

Program and financing

[In thousands of dollars]

	1961 actual	1962 estimate	1963 estimate
Program by activities:			
1. Grants and related contracts:			
(*a*) Research	34,623	78,233	100,409
(*b*) Fellowships	9,853	10,997	10,997
(*c*) Training	26,961	29,400	29,400
Total, grants and related contracts	71,437	118,630	140,806
2. Direct operations:			
(*a*) Biologics standards	2,702	2,809	4,000
(*b*) Review and approval of grants	1,207	1,842	2,379
(*c*) Administration	411	588	641
Total, direct operations	4,320	5,239	7,020
Total program costs [1]	75,757	123,869	147,826
Change in selected resources [2]	200	271	-------------
Total obligations	75,957	124,140	147,826
Financing:			
Comparative transfers to other accounts	7,615	412	-------------
Unobligated balance lapsing	328	3,037	-------------
New obligational authority	83,900	127,589	147,826
New obligational authority:			
Appropriation	83,900	127,637	147,826
Transferred to "Operating expenses, Public Buildings Service," General Services Administration (75 Stat. 353)	-------------	−48	-------------
Appropriation (adjusted)	83,900	127,589	147,826

[1] Includes capital outlay as follows: 1961, $114,000; 1962, $93,000; 1963, $142,000.

[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1960, $206,000 (1961 adjustments −$2,000); 1961, $404,000; 1962, $675,000; 1963, $675,000.

Mr. FOGARTY. All right. Dr. Hunt, are you ready?

Dr. HUNT. Yes, sir.

GENERAL STATEMENT

Mr. FOGARTY. All right; you may go ahead. Do you have a statement for the committee?

Dr. HUNT. We have submitted a statement, Mr. Chairman.

Mr. FOGARTY. All right; we shall put that in the record, and you may summarize.

(The complete statement of Dr. Hunt follows:)

STATEMENT BY CHIEF, DIVISION OF GENERAL MEDICAL SCIENCES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, ON "GENERAL RESEARCH AND SERVICES, NATIONAL INSTITUTE OF HEALTH"

Mr. Chairman and members of the committee, my statement is on behalf of the Division of General Medical Sciences. The other Division supported by this appropriation, the Division of Biologics Standards, has been discussed by the Director of the National Institutes of Health in his opening statement.

The Division of General Medical Sciences administers the NIH grant programs for research in the sciences basic to medicine and biology, in public health, and on certain clinical problems not covered by the programs of the institutes. In addition, the Division administers the grant programs for training investigators in the basic biomedical sciences, provides fellowships for research training and directs the NIH Center for Aging Research, the general clinical research center program, the general research support grant program, and the Center for Research in Child Health. I would like to discuss the several parts of each of these two principal areas: research and research training.

RESEARCH ACTIVITIES

In the historical perspective, man has been concerned about his health ever since his earliest development of orderly thought processes. There is evidence that even neolithic man performed a type of brain surgery and ancient Egyptian records indicate the uses of various potions to treat injuries and diseases 5,500 years ago.

Despite this early start, the course of medical progress has not been a straight line between knowledge and action, or between proper diagnosis and proper therapy. Like so many of man's efforts to grow and develop it has been halting and disorderly. While Aristotle discoursed in 300 B.C. on what today would be called anatomy and zoology, and Galen made influential anatomical observations in A.D. 100 there had been little progress 1,300 years later in the middle ages when physicians often ignored the wounds of soldiers and administered a form of medical treatment to their weapons instead.

The most significant advances in medicine have been made during the past 300 years, and the past 50 years, beyond doubt, are those of which physicians and medical scientists are the most proud. For it would seem that the medical sciences are gaining control over many of the extrinsic factors adversely affecting man's health, such as pathogenic bacteria and parasites. Man has been given a new freedom from infectious disease. At the same time, there has been considerable progress in relieving man of the pain and stress of diseases caused by or involving intrinsic factors, such as diabetes, types of anemia, nutritional disorders. Medical progress permits man to live with serious physical disablements.

Despite this great progress, the medical scientists today cannot relax in comfort with what he has already learned. He is deeply conscious of what he does not know, of what he has not yet been able to accomplish. Most of his difficulties and most of his opportunities for advancement involve fundamental biomedical research, without which medical progress would be impossible.

The encouragement and support of basic biomedical research is the principal assignment of both the research and research training programs of the Division of General Medical Sciences. It should be noted that the research activities being supported by the Division are not concerned solely with the definition of normal biological processes. These activities also are aiding in the definition of disease processes and in distinguishing between disease processes and the processes of aging. They are providing data which are essential tools in other types of research, both fundamental and clinical. They are providing information relative to the effects on man of new drugs and other forms of therapy, and they are contributing to the development of new medical procedures, instrumentation, and communications.

All of these efforts involve the pursuit of knowledge of biological processes ranging from the molecular to the social level, and this pursuit can be divided generally into the four principal areas of research at (1) the cellular and subcellular levels, (2) the tissues and organs, (3) physical structure and function of the whole person or animal, and (4) the behavior of the person or animal as a complex of integrated functions.

Time does not permit an elaborate discussion of all of these, but I would like to speak to the two extremes; i.e., the cells on one hand and the behavioral sciences on the other.

Ancient biologists and physicians thought they had made great progress with gross observations about the location and structure of human organs and muscles and bones. Demonstrations of the circulation of the blood in the early 17th century were considered striking advancements. It was only 123 years ago that it was determined that plants and animals are formed of cells; and it was with this development, permitted by the invention of the microscope, that man first began to realize with some certainty that many of the secrets of life and growth and disease are locked within these minute masses of protoplasm, each with a nucleus and each capable of amazing action and interaction; and it was then medical science realized that it must learn how and why these cells are formed, their constituents, how and why they grow normally or abnormally, how they interact.

The importance of this work applies across the entire spectrum of biomedical research. It applies to research in muscle tissues, as directly involved in studies of many types of heart disease; it applies to cancer in studies of how and why cells reproduce abnormally.

All conditions and functions of all parts of the human body depend on vast numbers of complex chemical processes and reactions. Scientists have been able to trace these processes to the cells and to a series of casual sequences within the cells. But precise and complete information as to the exact mechanisms involved still eludes us. More knowledge is critically needed in relation to a great variety of studies in biochemistry, and a better understanding of hormones and enzymes. and in studies of diseases such as anemias and diabetes.

Actually, basic studies of the cells from chemical and other standpoints, at the level of their molecules, could produce very striking advancements against a variety of other diseases. It may be that disturbed processes of the cell molecules are a major factor in the presence and nature of such widely diverse disorders as certain mental diseases, infertility, alcoholism, viral infections, and others. With further work, therefore, in molecular biology, it may be possible to strike an effective blow against these and many other disorders.

From the biological standpoint, the cell holds the answer to a great array of questions about human reproduction and genetics, many types of congenital malformations and growth problems in children and adults, the processes of aging, and even death.

In the success of scientists over the years in cutting the cell apart, they have learned of the presence of many of its major components. Learning how these components function and interact is the immense challenge. Great progress has been made, as recognized in the award of Nobel Prizes in recent years, in the field of genetics. One major question is how the gene, which is contained within the cell, stores and transmits its information. It seems probable that the DNA (deoxyribonucleic acid) protein, contained within the gene, does this: it seems that this protein governs the characteristics of the cell and thus the whole man. But vast amounts of work remain to be done. The importance of this can be seen in the fact that it is these mechanisms which control the intelligence, temperament, bodily vigor, longevity, and disease tendencies or resistance, and behavior of man. These mechanisms also bear on the processes by which certain injuries, such as those caused by radiation, are transmitted from one generation to another.

This type of research may permit medical science some day to exert an influence over the genes, helping to prevent or relieve certain human disorders. With other types of research in human development, it may become possible to provide greater prenatal safety for the mother, a further decrease in fetal and infant abnormalities and increased safety for the child, particularly during its first critical year.

In considering the behavioral sciences we find a growing need for information on how and why man conducts himself as he does within his human and technological environments and how and why he develops and changes.

There has been much research and progress in the behavioral sciences in mental illness and psychiatry. The National Institute of Mental Health, for example, carries out and supports extensive research in the behavioral sciences in relation to its mission. So far, however, there has been relatively little progress in translating the present body of knowledge in the behavioral sciences to help the individual consciously and successfully achieve productivity and well-being under the stresses of life.

The National Institutes of Health is intensifying its work in the behavioral sciences; and this Division has been assigned responsibility for encouraging and supporting research and research training in the basic areas, as distinguished from the categorical interests of the Institutes, including, for example, experimental and physiological psychology, cultural and comparative anthropology, sociology, cognition, motivation, social medicine, ethnic relationships, and the physical correlates of behavior.

The increasing needs for research in these areas arise from a number of conditions. There is, first of all, the continuing effort to understand man fully, from the genetic blueprint which fashioned him, to his attitude, for example, toward his job. But there are other, more specific conditions, such as the health problems forced by the new technology of this age, creating new environmental hazards to health. For a solution, these problems depend on a determination of the conditions making for changes in personal and community habits and attitudes.

Beyond these points are the medical needs for increasing consideration of the entire human being—his mental posture as well as physical condition, his climatic, work and home environments, and his economic and social status. This "whole man" approach can be critically important in diagnosing and treating his illnesses and in making prognoses of his future health and medical care needs. Medical needs also could include work in communications and motivation in relation to national medical problems where public acceptance is important. Polio vaccination and water fluoridation are examples of such problems.

The convergence of the behavioral sciences with other biomedical sciences, begins at the most basic level—that is, with genetics, and the genetic factors and/or other inborn conditions, such as those affecting the embryo and fetus, which affect growth and development and temperament. It is known that in some respects man's behavior can be an expression of his physiological makeup, but as yet there has been very little work in taking the next step—that is, to establish scientifically adequate correlations between behavioral phenomena and the basic biological sciences. This work would bear on the needs to know more about the aspects of man's behavior which cause disease and more about the effects of disease on man's behavior.

Fields receiving new emphasis, in addition to the basic behavioral sciences, include biomedical engineering and biophysics.

In summary, as of the end of calendar year 1961, the Division was supporting approximately 1,420 research grant projects as follows:

	Number	Amount
Basic biomedical sciences	1,100	$20,292,369
Clinical sciences	139	3,656,188
Public health, medical care, and nursing	90	3,348,329
Methods and tools of science	91	3,580,612
Total	1,420	30,877,498

Clinical research centers

Under the general clinical research center program, which was inaugurated about 2 years ago, grants have been made to establish 40 centers at medical schools and research hospitals across the country. They will provide a total of 535 beds for research patients. Applications for funds to support additional centers have been received in the Division and are being processed.

This program, which was established at the direction of the Congress, has the overall purpose of helping to intensify and improve medical research at the clinical level.

In recent years clinical research in the Nation has not been considered adequate, largely because of a lack of facilities for the highly specialized and accurate observations and measurements increasingly needed in clinical research.

The general clinical research centers supported by this program (1) aid in creating a cohesive force for clinical investigation within a medical school or hospital in which several departments may participate; (2) encourage better integrated interdisciplinary research; (3) provide opportunities for catalysts of research ideas among different investigators; (4) offer basic scientists maximum potential for clinical research; (5) offer research opportunities for those departments of a medical school not yet well established in research; and (6) afford a model of excellence for clinical research and clinical research training within an appropriate institution.

Of the 40 institutions which have been awarded grant funds for centers, a number are just getting underway. Several, however, have been in operation for a year and some for a year and a half.

The specific research projects they are carrying out are too great in number to be recited here, but I would like to mention a few. These include: studies of the pituitary and adrenal glands, cirrhosis of the liver, dwarfism, medical genetics, aplastic anemia, kidney diseases, and children with neurological disorders which make them indifferent to pain.

The impact of the program on the grantee institutions already is considered a tremendous one, not only in terms of opportunities for research and training but also in terms of new channels of communication on research approaches among departments within medical schools.

General research support grants program

The general research support grants program was authorized by an amendment to the Public Health Service Act in September 1960, and is being inaugurated in this fiscal year. The program, like the individual project grants of NIH, has the purpose of supporting the research and research training efforts of schools and other institutions in the health-related sciences. The principal difference is that under a general research support grant, the institution has considerable freedom in determining the research and research-training uses to which the funds will be put within the policies prescribed by the Public Health Service in accordance with the law. The new legislation does not give the Public Health Service any expanded authority to support new types of expenditures for research and research training.

The law authorizes support to "public or nonprofit universities, hospitals, laboratories, and other institutions." For the first year of the program's operation, general research support grants are being made only to eligible schools of medicine, dentistry, osteopathy, and public health—a total of 153 institutions. Extension of the program to other research institutions is planned for 1963.

Administrative responsibility for the program was assigned to the Division of General Medical Sciences in July 1961. By August, information statements had been distributed to all schools. By September, application forms had been developed and sent to all schools. By the end of October, all 153 eligible institutions had submitted applications and in January 1962 the awards had been made.

The amount of each grant was determined on the basis of a formula which takes into account the research support the institution is receiving from NIH and other Federal Government programs and from non-Federal sources.

An idea of how we expect these funds to be used is provided by an excerpt from the information material distributed by this Division for the guidance of applying institutions.

"It is expected that the grants will be used for four principal kinds of research and research training activities:

"1. Support of resources; for example, the operation of central research resources, such as animal facilities, not related solely to any one specific project or program but essential to the entire health related research activity of the institution (care should be exercised to insure that these costs are not also charged to other Public Health Service grants); the provision of ancillary research services, such as shopwork.

"2. Support of personnel; especially the provision of stable salary support for staff members engaged in research and research training whose salaries would otherwise be dependent on individual research grants or similar less stable sources. Any payments of stipends to trainees should be in accordance with Public Health Service policies.

"3. Support of projects; for example, the support of promising ideas that require further exploration and development prior to more formal consideration for project support; the payment of unexpected expenses in an established project.

"4. Support of certain activities now covered by Public Health Service grants, for which support will no longer be available on an individual basis; for example, research grants for less than $2,000 in 1 year; supplemental grants during an active grant year for salary increases; grants for student part-time and post-sophomore training programs."

The applications submitted by the eligible schools indicate that they do plan to use the funds in these ways.

Center for research in child health

Last year the Surgeon General approved the establishment of a Center for Research in Child Health in the Division of General Medical Sciences. The center will have the following responsibilities: (1) Directing a program aimed at encouraging and stimulating developmental and exploratory research and research training activities in the basic biological, behavioral, and clinical sciences related to the phenomena and health problems of childhood and adolescence: (2) strengthening the role of the National Institutes of Health in the multidisciplinary fields related to child health, growth, and development, both intramurally and extramurally, through consultation and advice to the several categorical Institutes; (3) providing a central point for the development, coordination, and dissemination of information concerning the character, status of, and needs for, research and research training in fields related to child health; (4) administering broad collaborative research programs and performing national service center functions in support thereof; (5) sponsoring conferences.

symposia, and seminars in matters relating to research and research training in the field of child health. Organization of the center is in process, and a director has recently been appointed.

Center for aging research

Another component of the Division originally established in 1956, is the Center for Aging Research. In recognition of the problems attending the increase in the number of older persons in our society, the Center for Aging Research serves as a focal point for the rather extensive research programs being carried out and supported by the Institutes of NIH and by this Division. The moneys for these programs in aging come from the appropriations to each Institute and this Division, with the Center for Aging Research serving as a central information unit on these activities. The center also stimulates and assists in the development of new research projects in gerontology and geriatrics at universities, medical centers, and various other research institutions in this country and abroad.

In addition to the grant programs being supported by all of the Institutes and this Division, two Institutes, the National Heart Institute and the National Institute of Mental Health, have intramural programs carried on with NIH scientists and facilities.

The spectrum of research goals of all of the NIH aging programs is quite broad, ranging from the basic biochemical processes of aging, at one extreme, to research in rehabilitation techniques at the other.

Interest in the field of aging continues to grow among scientists of many specialties. As an indication of this I would like to read a few figures on the growth in the number of grant projects, and the dollar expenditures involved, over the past 5 years. In each case, these measurements are as of January 31 of that year.

Year	Number of projects	Dollar level (million)
1958	274	$4.5
1959	404	7.7
1960	582	12.4
1961	700	16.2
1962	879	30.4

RESEARCH TRAINING ACTIVITIES

Research training activities in the basic biomedical sciences necessarily represent a long-range investment in the scientific future of the Nation and must be planned and balanced to meet future needs in research itself and in growing requirements for improvements in the quality and quantity of teachers.

In recognition of the unquestionable significance of basic research in man's pursuit of a more healthful existence, this Division's research training programs have the goal of helping to build an adequate supply of quality-trained basic biomedical scientists available for research, research training, and teaching in the fundamental health sciences as well as in important disease-oriented areas.

Thus the research training programs of this Division serve two major purposes: (1) to increase and enhance the potential of the training institutions across the Nation to provide better training in the basic biomedical sciences; and (2) to encourage and aid the flow of quality students through the graduate schools, in great part by enlarging the training opportunities for predoctoral and postdoctoral candidates.

It is at the predoctoral and postdoctoral levels of academic training that the important interdisciplinary perspective of the biomedical sciences can be impressed upon the developing investigator, and his training can be undertaken with a view toward the emerging fields of research endeavor. It is therefore possible to correlate future needs and opportunities with present training activities. Indeed, in consideration of the years necessary to train a research scientist, this is imperative.

The Division of General Medical Sciences approaches its responsibilities to support training in two ways. The first is through grants to institutions and the second is through fellowships to individuals. I would like to discuss each of these activities and their component parts.

Research training

In an effort to improve research training in the basic biomedical sciences, the research training program of the Division provides grant funds to appropriate institutions. These funds help defray the expenses of the institutions in providing the training program proposed, and provide subsistence stipends to trainees to permit them to participate in the program. From the standpoint of national need, the grants have the overall purposes of establishing, expanding or improving graduate and postdoctoral research training.

Training institutions are free to propose programs of any nature which best reflect particular research training needs and which provide the best grouping of the institution's facilities and abilities to satisfy these needs. The institutions are not restricted to any set plan or pattern in developing training programs. The excellence of training is the principal consideration, and this, of course, requires actual and extensive research experience.

At present the Division is operating regular programs in 11 areas: anatomical sciences, biochemistry, biometry (including biomathematics), biophysical sciences, developmental biology (including cell biology), epidemiology, genetics, microbiology, pathology, pharmacology, and physiology. Each of these programs functions under the guidance of a training committee composed of non-Federal scientists and other experts in the particular field in question.

In addition, upon the recommendations of the National Advisory Health Council and other expert scientific consultants, support is being provided for training in special fields which are becoming of increasing importance to research and to medicine. I would like to discuss four of these.

Basic behavioral sciences

Earlier I have discussed this field from the research standpoint. Training for research in this area is necessary to insure an adequate supply of appropriately trained investigators to carry out work in this enlarging field. Training of this basic nature will augment the programs of the National Institute of Mental Health, which necessarily are of a more specific and applied nature. The initial goal is the establishment of essential training in the fields of experimental and physiological psychology, cultural and comparative anthropology, and areas concerned with the integration and relationship of social systems. More investigators also should be trained to work in the fields of psychoacoustics, cognition, motivation, social medicine, ethnic relationships, and the factors dealing with communications within cultural communities and societies.

Basic developmental sciences

The basic developmental sciences relate to a broad multidisciplinary field. They cover the structural, chemical, regulatory, and functional aspects of the processes by which an organism begins with the gamete and develops into the adult. There are increasing needs for investigators trained in normal and abnormal processes of embryology and development and fields such as immunology, cellular physiology, placental and fetal physiology, and other related areas.

Biomedical engineering

In the simplest terms, biomedical engineering is concerned with measurement and control systems in relation to biological studies and medical procedures. The task of relating engineering principles to biology, however, is difficult because the two have developed over the years somewhat as separate sciences in relation to what, in the past, have been rather separate goals. In recent years there has been an expanding need for instrumentation in the medical and biological sciences in making large numbers of observations of many variables.

Biophysics

In one sense, the field of biophysics might be called the parent science of the field of biomedical engineering, which I have just discussed. As compared to biomedical engineering, biophysics is broader and more interdisciplinary and could be said to be more concerned with the development of basic theories of physics in relation to a variety of biomedical research efforts. Biophysics provides techniques and criteria for work in fields such as molecular biology, studies of the physical properties of macromolecules and their interactions. Biophysics also has great potential for helping scientists to learn more about the nervous system and the brain and the relationships in the human body—almost infinite in number—between structure and function.

In summary, I may say that at the end of calendar year 1961, the Division's research training activities were supporting approximately 500 separate training programs in medical schools and other educational institutions across the country in more than a score of basic biomedical sciencies. These programs are aiding in the support of approximately 4,500 individual students and scientists.

Medical student research training program

Following the 5-year successful test of the experimental training program, the Division last year established, on a regular basis, what is now called the medical student research training program. The grant funds provided under this program are not used to provide support for students during the regular courses of study required for the M.D. degree. The funds instead assist the medical schools in the early identification, selection, and research training of students who show promise for productive careers in academic medicine. The funds may be used for additional faculty, equipment, and supplies needed specifically for the research training activities, as well as for stipends permitting selected students to spend their summers in research or graduate study or to drop out of their regular courses for a year of more intensive research training. An additional advantage of the program is the encouragement and strengthening of the basic science areas of the schools by introducing new natural science disciplines, interests, and competencies, in order to provide future faculty members with the basic science foundations on which progress in medical educations, research, and practice must rest.

With this program entering its sixth year, it is possible at this point to make a sound evaluation of its value in relation to its specific goals. It has been successful beyond our expectations. It has aided the schools, by helping in the improvement of their curricular patterns, and it has helped both the schools and the students by encouraging and broadening their interest in academic medicine. An example of this is found in the amount and depth of research conducted by the medical students under this program. One school alone has provided us a record of more than 25 scientific papers published by students participating in this program.

The measure of this program is not primarily the research accomplished, however, but its success in providing future faculty members with the basic science foundations on which progress in medical education and practice as well as research, must rest.

RESEARCH FELLOWSHIPS

The second major activity within the Division's training responsibilities is in research fellowships.

Earlier I referred to the great importance of research training at the predoctoral and postdoctoral levels to help give the developing investigator an interdisciplinary perspective of the biomedical sciences and to aline his training in accord with the new, emerging fields of research effort. This requires a level of flexibility in planning and programing and we are seeking to meet this need in great part through the fellowship programs.

While the research training grants are made to institutions, the fellowship awards are made to individuals to provide specific support for new areas and to give special emphasis at a number of educational levels and situations.

Emphasis in this Division is placed on the basic biomedical sciences, such as anatomy, behavioral sciences, biochemistry, biomathematics, biostatistics, biophysical sciences, developmental biology, endocrinology, epidemiology, genetics, immunology, microbiology, pathology, pharmacology, physiology, and virology.

For some years we have been making several classes of fellowship awards: Predoctoral research fellowships, postdoctoral research fellowships; special fellowships; and special predoctoral fellowships in nursing research.

As of the end of calendar year 1961 the Division was assisting almost 2,000 students and scientists in acquiring advanced training.

Research career award program

The research career award program was initiated during the current fiscal year to provide increased numbers of stable career opportunities for qualified candidates of superior potential and capability in the health-related sciences. Two groups of awards are available, as follows:

Research career development awards—awards in this group are for young investigators who desire further training in a productive research environment as well as for scientists undertaking independent research who need further experience to qualify for senior positions. These awards are intended to finance positions for able scientists who plan to pursue careers in independent research and teaching. The candidate must have had at least 3 years of relevant research or professional experience following the doctoral degree and must have demonstrated promise for a career in independent research.

Research career development awards may be made for initial periods of 5 years and may be renewed upon adequate justification to provide a total period of support to an individual of not more than 10 years.

Research career awards—awards in this group are for experienced investigators in productive careers of independent research and teaching. These awards are intended to finance additional stable positions and are made on the basis of nationwide competition; the research standards expected of candidates are high. The candidate must have demonstrated an ability to pursue a career in independent research and his research must have won the respect of scientific leaders in his field.

Research career awards are made in 5-year increments with review at appropriate intervals to insure that the award continues to promote the objectives of the program. Awards are made with the firm intention to continue Federal support for the full career of the individual provided (1) the recipient continues to meet the standards set by the institution for scientists with substantial responsibilities for research and research training, and (2) the institution and the scientist wish to have the award continued.

Actual research experience is an indispensable part of research training. In considering the depth and effectiveness of our training and fellowship programs, it is therefore significant to consider the research work being conducted by our research training grantees and by the recipients of fellowship awards. In a separate document called Highlights of Research Progress in the General Medical Sciences, we have provided the committee a review of work by our research grantees. For the first time this year we have added a partial list of papers published under our training grants. It is significant that nearly a third of the total of about 800 papers were published by men in the course of their work under the training and fellowship programs.

CONCLUSION

In conclusion, Mr. Chairman, the request for the Division of General Medical Sciences for 1963 is $143,826,000, which will provide for an increase of $22,176,000 in research grants; an increase of $337,000 in review and approval for professional and clerical staff engaged in processing, analyzing, and managing research and training grants; an increase of $195,000 representing this Division's share of costs for review and approval and administrative services furnished centrally; and an increase of $37,000 for overall planning, direction, and coordination of the programs of this Division.

The request for 1963 is distributed among program activities as follows:

Grants and related contracts:	
Research	$100, 409, 000
Fellowships	10, 997, 000
Training	29, 400, 000
Subtotal, grants	140, 806, 000
Direct operations:	
Review and approval of grants	2, 379, 000
Administration	641, 000
Subtotal, direct operations	3, 020, 000
Total 1963 Division request	143, 826, 000

Dr. HUNT. I would like to summarize, if I may.

Mr. FOGARTY. All right, go ahead.

RESPONSIBILITY OF THE DIVISION

Dr. HUNT. Mr. Chairman and members of the committee: This statement is on behalf of the Division of General Medical Sciences, which administers the NIH grant programs for research in the sciences basic to medicine and biology, in public health, and on certain clinical problems not covered by the programs of the Institutes. The Division also administers the NIH grant programs for training investigators in the basic biomedical sciences, provides fellowships for general research training and directs the NIH Center for Aging Research, the General Clinical Research Center program, the Center for Research in Child Health and the new general research support grant program.

In the Division's grant programs for both research and research training, great emphasis is placed on the fundamental biomedical sciences. This is in recognition of the great significance that basic research bears in relation to many aspects of man's health. Basic research carries forth the unending pursuit of knowledge about the genetic origin, reproduction, precise structure, and behavior of life forms from the molecular level to social conduct. It aids materially in the definition of disease processes, in distinguishing between disease processes and the processes of aging, and in identifying normal as opposed to abnormal conditions and processes. It provides data which are essential tools in other types of research, both fundamental and clinical. It provides information relative to the effects on animals and humans of new drugs and other forms of therapy, and contributes to the development of new medical procedures.

RESEARCH GRANTS

As of the end of calendar year 1961, the Division was supporting a total of approximately 1,448 research grants. Of this number more than 60 percent are supporting projects in the basic biomedical sciences, with the balance supporting work in the clinical sciences, public health and the methods and tools of sciences. Fields receiving additional emphasis this year in research are the basic behavioral sciences, biomedical engineering, and biophysics.

TRAINING

In the research training and fellowship programs, activities to support the training of investigators are being carried out at a variety of academic levels in a large number of basic medical and biological disciplines. At the end of the calendar year, the Division was supporting approximately 500 separate research training programs in medical schools and other educational institutions. The activities were aiding in the support of approximately 4,500 individual students and scientists. The research fellowship programs were providing support for nearly 1,500 additional students and scientists. Areas receiving additional emphasis this year in research training include the basic behavioral sciences, the basic developmental sciences, biomedical engineering, and biophysics.

During the year the Division initiated the new general research support grants program. A total of 153 grants, totaling $20 million, was awarded to schools of medicine, dentistry, osteopathy, and public health.

Also during the year, further progress was made in the organization of the Center for Research in Child Health, including the appointment of a Director.

SUMMARY OF BUDGET INCREASES

In conclusion, Mr. Chairman, the request for the Division of General Medical Sciences for 1963 is $143,826,000 as compared with the $121,081,000 available in 1962. The request for 1963 will provide for an increase of $22,176,000 in research grants; an increase of $337,000 in review and approval for professional and clerical staff engaged in processing, analyzing, and managing research and training grants; an increase of $195,000 representing this Division's share of costs for review and approval and administrative services furnished centrally; and an increase of $37,000 for overall planning, direction, and coordination of the programs of this Division.

Mr. FOGARTY. Thank you, Doctor.

The appropriation for 1962 is $127,637,000, and the request for 1963 is $147,826,000. There are two comparative transfers to other appropriations totaling $460,000, so the real increase is $20,649,000.

Is that right?

Mr. SEGGEL. That is right, sir.

TRANSFERS FOR INTERNATIONAL RESEARCH CENTERS

Mr. FOGARTY. Now, I heard someone say there is also a transfer to this appropriation from other institutes regarding the international research centers. Is that right?

Dr. HUNT. Yes.

Mr. FOGARTY. Give us the figure. What is the figure?

Dr. HUNT. This is a program that Dr. Shannon described earlier.

Mr. FOGARTY. Yes, I know the program but what is the figure?

Dr. HUNT. Excuse me; $2,984,000.

Mr. FOGARTY. Where does this show up in your summary tables?

I am looking at page 4. Is that not the table you have submitted that is supposed to set forth all significant changes in your budget?

Dr. HUNT. It is on page 7, Mr. Chairman, under the heading, "Explanation of changes," and the subheading "Research grants," the next to the last sentence. The amount is $2,984,000, which will provide support for international centers for medical research and training.

Mr. FOGARTY. Where does it say anything about this being transferred to this division?

Dr. HUNT. This is what I could not find a minute ago. I do not know.

Mr. FOGARTY. I would think it would show up in your budget table.

Mr. KELLY. That accounts for an increase of 1963 over 1962. It is not a comparative transfer.

Mr. SEGGEL. It was handled as a nonrecurring cost in each of the categories, where it was previously financed, and as an add-on for 1963 in this appropriation.

Mr. FOGARTY. It has been brought to my attention that in the Cancer justifications, you spell it right out, "Transfers to other accounts, international centers for medical research and training"—$369,000.

Mr. SEGGEL. Is that not reflected as a nonrecurring cost to the Cancer Institute—that is, as a cost not carried forward in 1963?

Dr. SHANNON. Mr. Chairman, could we straighten this out and give it to you in the form of a note? Because the mechanics of the budget are such that in certain cases, it is split into two, as I recall. Part of it is transferred to allergy and infectious diseases and the remainder appears here in the general appropriation.

Is that not it?

Mr. FOGARTY. Well, you do not show it in your summary table, and you just mention it in the narrative justifications. Why is that?

Mr. SEGGEL. Mr. Chairman, on page 57 of the justifications, it indicates in Cancer that the increase consists of a gross increase of $9,263,000 reduced by $259,000 representing a transfer. So what we have done is deduct the international item for 1963 from the Cancer appropriation, as well as other categorical appropriations.

Mr. FOGARTY. How do you account for the fact that Cancer says it is "Transfers to other accounts: international centers for medical research and training," but for the Division of General Research and Services you say it is not a transfer?

Mr. SEGGEL. You see, you have gross increases of $13,527,000 and gross decreases of $2,000,000 for a net of $11,524,000.

Mr. FOGARTY. All right.

Mr. SEGGEL. The decreases in the Cancer appropriations include the charges to 1962 for the international centers that are not carried in 1963.

Mr. FOGARTY. All right. Now show me where this comparable increase is in the table for the Division of General Research and Services.

Mr. SEGGEL. Well, it is reflected as an add-on in research grants in the general research and services appropriation.

Mr. FOGARTY. Are you trying to lose this?

Dr. SHANNON. No, sir; we are trying to pull it together.

Mr. FOGARTY. It looks to me as though somebody is trying to hide it, either you or the Bureau of the Budget.

Dr. SHANNON. No, sir. If it has the appearance of being hidden, it is our error; but it is not our intent.

What we are trying to do here, is to bring these things together in an identifiable single item because they represent a single activity, rather than spread them across all appropriations.

Dr. HUNT. Mr. Chairman, it does show in the table on page 20 as a line item showing an increase from $208,000 to $3,192,000, a net increase of $2,984,000.

Mr. FOGARTY. Now, in that table, too, you do not say anything about a transfer from the other Institutes.

Dr. HUNT. No. The word "transfer" inadvertently got into the discussion, I am afraid. It is not a transfer. It shows as a net increase here.

Mr. FOGARTY. Well, the Cancer one is wrong, is that it? They call it a transfer.

Mr. SEGGEL. I do not know whether "transfer" is the proper technical word for it, but the fact is that the costs are dropped from the several categorical appropriations and the total added onto the general appropriation. That is what this is intended to indicate.

Mr. FOGARTY. What happens if the committee decides that this should not be transferred?

Mr. KELLY. If you wanted to arrive at the same amount in the budget, you would have to adjust the amount of the request to put it back where it was.

Mr. FOGARTY. But how can we adjust it in view of the justifications for general research? The justification doesn't tell us which Institutes this was transferred from, much less the amount from each.

Mr. KELLY. We have great confidence in the staff assistant to the committee to accomplish that, Mr. Chairman.

Mr. FOGARTY. Is there anything in the justifications that we can look to?

Mr. KELLY. Well, you seem to have found it.

REASON FOR TRANSFERS

Mr. FOGARTY. Just why are you centering them all under "General research and services?"

Dr. SHANNON. Primarily so that the Division of General Medical Sciences shall be responsible for a budget item that appears in a single place, rather than for a budget item that is composed of a series of individual sums in each of the appropriations.

This is something of more than theoretical importance, because, if sums appear in the appropriations for each of the categorical Institutes, which, together, make up the total for the purpose of program operation, then any grant that is paid out of the total must have council approval for each of the Institutes that contribute dollars.

This then becomes a very cumbersome program to develop, because each grant that participates in the total sum must be presented to each of several councils, or however many councils are involved.

Under the proposed arrangement it will be possible to present the total package to a single council, namely, the National Advisory Health Council, and their action then will be definitive and final.

RESERVE OF 1962 APPROPRIATIONS

Mr. FOGARTY. Your reserve is $3,037,000. How much of this is forced savings?

Dr. HUNT. The full amount, Mr. Chairman.

Mr. FOGARTY. The full amount.

EFFECT ON RESEARCH GRANTS

How does this affect your research grant program for 1962?

Dr. HUNT. The reserve is distributed as follows: $874,000 for research grants which includes $500,000 for one general clinical research center, and $374,000 for the support of approximately 15 to 20 additional research projects; $293,000 for fellowships, which would support in the neighborhood of 80 additional fellows; and $1.6 million for training which would support about 150 additional trainees.

The balance of reserves was in administration and review and approval of grants activities.

Mr. FOGARTY. You really got quite a cut, then. If you had that $3 million released, you would be able to finance all of the projects you have approved, is that right?

Dr. HUNT. Yes, sir; that is correct.

Mr. FOGARTY. You are in really bad shape.

EFFECT OF TRAINING

How much is taken from the training program?

Dr. HUNT. $1.6 million from training.

Mr. FOGARTY. I thought you told us that training is one of the areas where you really needed to expand. Have you changed your mind?

Dr HUNT. No, sir.

Mr. FOGARTY. You still think that this is necessary?

Dr. HUNT. We do.

Mr. FOGARTY. Why?

Dr. HUNT. The manpower study which Dr. Shannon spoke of earlier in his testimony has reinforced and put on a more definitive basis the feeling we have had that there was both need and an opportunity for expanding the training programs in the basic biomedical sciences.

Mr. FOGARTY. Do you think there is additional training potential that is not being used?

Dr. HUNT. Yes, sir.

Mr. FOGARTY. And there is a shortage of trained personnel in this field?

Dr. HUNT. Yes, sir.

Mr. FOGARTY. The President said:

> I would prefer that obligational authority remain uncommitted where there is any doubt that expenditures would yield substantial returns to the national interest.

Is there any doubt in your mind that, if these funds were released, they would yield substantial returns to the national interest?

Dr. HUNT. I cannot take an opposite stand; no, sir.

Mr. FOGARTY. What is that?

Dr. HUNT. I cannot take an opposite stand.

Mr. FOGARTY. What do you mean; opposite to me or the President?

Dr. HUNT. The question you asked.

Mr. FOGARTY. Oh, you agree, then?

Dr. HUNT. Yes, sir.

Mr. FOGARTY. I have had all kinds of answers to that question when I put it to the witnesses, but you come up with a new one. You do agree.

Dr. HUNT. Yes, sir.

Mr. FOGARTY. That if these funds were released they would yield substantial returns to the national interest?

Dr. HUNT. I think that is a fair statement.

NEW AND EXPANDED RESEARCH GRANT PROGRAMS

Mr. FOGARTY. Almost all the increases are in research grants and related expenditures. Are you anticipating any new types of programs, or is this just an expansion of existing programs?

Dr. HUNT. We are doing both. We are expanding existing programs. We will have new emphasis on areas of research, which are being supported to a minor degree at present. There is nothing which is completely new.

But the biomedical engineering, computer research, and biophysics fields will all receive additional emphasis. We are planning to put a good deal of emphasis on basic research in the behavioral sciences.

Mr. Fogarty. What about the new programs?

Dr. Hunt. Well, research in the behavioral sciences comes closest to being a completely new one.

FUNDING APPROVED GRANTS

Mr. Fogarty. How many approved grants will you not be able to pay in 1963 under this budget you have?

I have it in front of me. There will be 222 and will amount to $5,830,000. You are going to be that much short under this budget.

Is it not also a fact that when you estimate for the future, you have always been on the conservative side as to the number of grants that would be submitted and approved in the following year?

Dr. Hunt. I think that that has been the case in this program.

Mr. Fogarty. This 222 figure should be considered a conservative figure?

Dr. Hunt. Yes, sir.

Mr. Fogarty. It probably will be more.

FELLOWSHIP PROGRAM

Now, you do not show any increase for fellowships or training. I thought you said this was a real problem.

Dr. Hunt. This is related to the overall policy of developing the manpower study before deciding which training programs should be expanded in 1963.

Mr. Fogarty. But you are taking another look at that now?

Dr. Hunt. Yes, sir.

Mr. Fogarty. And we should have some idea in a couple of weeks about what should be done in this area, in view of this report that you have?

Dr. Hunt. Yes, sir.

Mr. Laird. Mr. Chairman, could I ask a question?

Mr. Fogarty. Yes.

Mr. Laird. Is my understanding correct that we are going to get a budget amendment in this area on the basis of some report?

Dr. Hunt. No, sir.

Mr. Fogarty. I asked Dr. Shannon this morning to try to get up a table that would show how much is needed in addition to the budget to get this program in line with the report's recommendations. He said that would take them a couple of weeks.

BIOLOGICS STANDARDS

There is also an increase for biologics standards work. Who wants to tell us about this?

Dr. Shannon. I would be glad to take that up, Mr. Fogarty; or Dr. Mider, perhaps, who is directly responsible for it.

Mr. Fogarty. All right, either one of you.

First we shall place the prepared statement in the record.

(Dr. Shannon's prepared statement follows:)

DIVISION OF BIOLOGICS STANDARDS

GENERAL MISSION

The Federal Government's responsibility for the control of biological products began on July 1, 1902, with the passage by the Congress of an act to regulate the sale in interstate commerce of all viruses, serums, toxins, and analogous products applicable to the prevention and cure of diseases of man. The statute, now a part of the Public Health Service Act, is basically the same as in 1902 when the technical responsibilities of the biologics program were assigned to the National Institutes of Health, then known as the Hygienic Laboratory.

In 1937, the Laboratory of Biologics Control was created within the National Institutes of Health, and in 1948 it was made part of the National Microbiological Institute. In June 1955, authority was granted the Surgeon General by the Secretary of Health, Education, and Welfare to expand the biologics control function of the Public Health Service to the status of a separate division within the National Institutes of Health, called the Division of Biologics Standards. Its funds are derived from the appropriation "General research and services, NIH," which also finances the Division of General Medical Sciences.

The primary function of the Division is to administer those provisions of the Public Health Service Act pertaining to the safety, purity, and potency of such biological products as vaccines, antitoxins, therapeutic serums, and human blood and its derivatives.

There continues to be a significant increase in the volume and diversity of biological products due to the rapid scientific advance being made in the fields of microbiology and immunology. With the greater emphasis being placed upon reesarch by industry, the development of new products is proceeding at an accelerated rate. To meet this situation, DBS must continue to expand its control operations and must augment its research facilities to develop new lines of investigations within its program.

Control activities

The statute bases the control of biological products upon a system of licensing. This system includes the issuance of both establishment licenses and product licenses, following determination by DBS that the prescribed standards for safety, purity, and potency have been met. These standards are set forth in regulations which are continually reviewed for adequacy in the light of new advances. As new products are developed, additional standards are formulated.

As of December 31, 1961, 194 establishment licenses and 1,217 product licenses were in effect, the latter covering 284 specific products.

A major activity within the control program centers around the determination of the eligibility of establishments and of individual biological products for licensing. Prior to licensing, the manufacturer's physical facilities are inspected, operating procedures observed, the scientific and professional qualifications of his personnel are reviewed, all data which he is required to furnish with his application are carefully evaluated and representative samples of his product are tested. Once a product is licensed, continuing surveillance is maintained through the review of manufacturer's records of production and testing, and the testing in DBS laboratories of representative samples of these products. Tests, ranging from relatively simple sterility tests to complex and costly potency determinations and safety tests, many of which require the skills of specially trained professional personnel, are carried out each year in DBS laboratories on more than 5,000 individual lots of a wide variety of biological products.

In addition to inspection of manufacturing facilities and procedures prior to licensing, each licensed establishment is inspected annually to insure continuous compliance with prescribed standards. Close liaison is maintained with representatives of professional and technical staffs regarding proposed facilities, modification of existing facilities, or changes in production methods, insofar as they affect the safety, purity, and potency of the biological products for which they are licensed.

To assure that each licensed product is consistently of acceptable and uniform potency, standard physical reference preparations are developed and distributed by DBS to manufacturers and laboratories engaged in the standardization of biological products. With the rapidity with which new and improved products are being developed, this activity has become increasingly time consuming and costly for the Division. Seventy-three such preparations are now maintained and approximately 4,000 vials are distributed annually to research and control laboratories of licensed manufacturers, health departments, and universities in this country and abroad.

Scientific personnel of DBS and industry meet frequently to discuss problems of mutual scientific and technical interest. In addition, conferences are held with technical representatives of individual manufacturers concerning testing problems and production difficulties peculiar to their own organizations which might affect the safety, purity, and potency of the product. Through such cooperation with industry, as well as with independent investigators throughout the country, DBS is frequently able to identify potential problem areas in production and control before serious difficulties can arise.

DBS scientists, serving as members of international study groups, continue to take an active part in the World Health Organization's program for the development of international uniformity of biological products. During the past year over 150 scientists from foreign countries have spent from 1 day to several months in the Division studying methods of testing and control of biological products.

As a regulatory agency the DBS must be prepared on short notice to invest heavily both in man-days and in dollars in its enforcement activities. On the basis of findings uncovered during routine inspection and surveillance activities, scientists of the Division during the fall and winter of 1961 conducted an extensive investigation into irregularities involving the processing and distribution of blood and blood plasma in the New York area. Several hundred man-hours were spent in investigating and collecting evidence on the updating of human blood for transfusion and the processing and shipment of blood plasma by an unlicensed establishment. Close liaison was maintained with the Justice Department to whom all findings were submitted. An 80-count indictment was returned by a Federal grand jury in Manhattan on January 25, 1962, in connection with charges of changing the labels on outdated human blood.

Because of the highly technical nature of such problems, investigations of this type must be conducted by individuals with professional knowledge working with persons trained in the legal aspects of enforcement procedures. Since such violations present a definite hazard to the public, prompt and thorough action is required.

Research activities

The DBS conducts an active research program, which enables the Division to keep pace with the development of new and improved immunizing agents and to prepare physical references as well as to develop testing procedures for these products once they are ready for commercial production. Research is particularly active during the developmental and early production phases of new products. However, on occasion, extensive research is required in connection with a previously licensed and well-established product. During the past year this occurred when it was found that the recently discovered monkey virus, SV–40 was a contaminant of certain lots of inactivated (Salk) poliomyelitis vaccine. Adequate tests to determine the presence of this agent were developed by DBS and since May 1961 no vaccine has been released unless it has been shown to be free of SV–40. The Division's ability to mount large-scale testing for this agent long before any manufacturer was tooled up to do so made possible the continuing flow of poliomyelitis vaccine to physicians during the summer of 1961.

The extensive developmental research carried on during the past 2 years on live poliovirus vaccine culminated in the establishment of standards governing the production and testing of this vaccine which were published in the Federal Register on March 25, 1961. Later in the year, one establishment was licensed for the production of type 1 and type 2 oral vaccine. The DBS program on live poliovirus vaccine now combines control activities to insure the continued safety, purity, and potency of all lots of the licensed products as they reach the commercial market with an accelerated program designed to solve the problems concerning type 3 which have so far delayed the qualifying of this type for licensing.

Industry continues to attempt to meet the demand by the medical profession for multiple antigens which will immunize against several diseases simultaneously, although the preparation of such multiple antigens is a complex process. This is especially true of the so-called quadruple antigen vaccine containing diphtheria and tetanus toxoids and pertussis and poliomyelitis vaccines which is used extensively in pediatric practice. In 1961 studies conducted by DBS on the stability of this product revealed that there was a significant decrease in the potency of the pertussis component during the prescribed dating period. As a result of these investigations the dating period for this product was shortened and the potency requirement of the pertussis component was increased in order to insure that the potency does not fall below the established minimum level during the dating period even when the product is exposed to the normal variable conditions on the market.

Broad-based, comprehensive studies directed toward the improvement of testing procedures for the control of biological products derived from blood are being continued, including investigations covering all phases of blood collection, processing, shipment and storage.

Reports given at the NIH-University of Colorado sponsored International Conference on Measles Immunization in November indicated encouraging progress in the development of a satisfactory immunizing agent against measles. The development and the ultimate licensing of measles vaccines are complicated not only by the problem of adventitious agents, analogous to the SV–40 problem already noted in connection with poliomyelitis vaccine, but because of the simultaneous development of live virus vaccine to be used with gamma globulin, live virus vaccine to be used without gamma globulin, and inactivated measles vaccine produced in tissue cultures derived from a variety of animals. Each of these types of measles vaccine presents not only the problems common to all tissue culture vaccines, but each also gives rise to additional problems of a specific nature which will require extensive investigative work mostly in the field of general virology. These studies will include those which are designed to identify the problems as they relate to vaccine safety and to develop adequate test procedures to assure the continued safety, purity, and potency of the product. The development of these procedures is necessary before such products can be licensed; thereafter they become a part of the continuing monitoring and testing program of the Division.

The availability of monkeys which are susceptible to measles virus is an important need in the testing of the early lots of measles vaccine. This will entail special procurement, handling, and transportation of these animals followed by special quarantine and conditioning requirements prior to and during their use in measles vaccine studies. Past experience has shown that while monkeys are susceptible to measles infection in their natural environment, the nature of measles virus is such that the contact with other monkeys and with human beings, which occurs with present procurement and shipping methods, results in a situation in which almost all of the animals develop antibodies and thus resistance to measles infection by the time they reach the using laboratory. The same principle may also apply in the case of other virus vaccines, such as a vaccine for infectious hepatitis which may become imminent in the foreseeable future. In this particular case, there is a strong possibility that chimpanzees may play a role as test animals.

DBS is expanding its studies relating to the development of standard measles reference preparations, the standardization of techniques appropriate for effective evaluation of a measles vaccine, the standardization of gamma globulin for measles antibody content, and the drafting of recommended requirements for production and testing of measles vaccines.

During 1962 the resources of the Division were severely taxed by this growing workload and it was possible to meet these increased demands only by diverting personnel and resources from other projects of lower priority and by postponing investigations in other areas.

The large-scale support which has been given to medical research in recent years is now being reflected in the expanding development of new methods of immunization and therapy. The increasing public interest in new research findings has given competitive stimulus to hasten the development of products to be used for such purposes, thus materially reducing the time interval between research and product availability. The Division, charged with the responsibility to develop standards for these products, in turn, must concurrently expand its own research, testing, and control efforts in order to minimize delay in determining whether such products meet standards for safety, purity, and potency and thus facilitate the availability of satisfactory products at the earliest possible date.

The application of new tissue culture systems to vaccine production and the recent widespread interest in live vaccines has complicated and expanded the testing procedures required for such products. The concern of both the scientific community and the public over the role of viruses in the production of tumors has given additional importance to the problem of adventitious agents in vaccines produced in tissue cultures. The Division must continue to expand its programs on the development of tests to insure that licensed products are free of such extraneous viruses, as well as to increase its testing programs on such products.

Although laboratory testing space, including quarters for experimental animals, appeared adequate with the move in 1961 to the new Biologics Standards Building, requirements for new programs in 1962, particularly live poliovirus vaccine and measles vaccine, have increased considerably. In the 1963 estimate, $150,000 is included in the PHS "Buildings and facilities" appropriation for planning of a Biologics Standards Annex at Bethesda. Since $200,000 will be available in 1962 through transfer from other construction accounts, total planning and specifications will amount to $350,000 by 1963. Until the annex is available the Division will temporarily house its overflow in other Bethesda space and in rented space, if necessary.

The 1963 estimate includes funds for a contract program in applied research, as opposed to academic research, to supplement the Division's research and control programs. The Division further proposes to expand the viral vaccine program in an attempt to meet research needs, including tissue culture, pathology requirements, and animal research. The task of regulating the biologics under the control of the Division has become more complex with the development of the newer products. Consequently, there will be greater emphasis given to the control and enforcement activities of the Division.

Dr. Mider. Mr. Chairman, while the Division of Biologics Standards does have a small research program in relationship to its mission, its major activities are dictated by the provisions of the Public Health Service Act and the Public Health Service regulations pertaining to the control of biological products.

DEVELOPMENT OF EFFECTIVE POLIO VACCINES

As the committee is well aware, we have had a number of problems related to the development of effective polio vaccines. The killed vaccine is now in production and is found to be extremely useful. Types 1 and 2 of the live vaccines have been licensed. They are more easy to administer than the Salk type of vaccine.

A vaccine for type 3 has not yet been licensed because of difficulties in the stability of the organism with particular reference to its virulence for the central nervous system of monkeys.

The problem of viruses that have only been recently discovered or not known to exist in monkeys, and to some extent in human beings, have caused a reevaluation not only of the live polio virus vaccine but of other live vaccines such as those against adenoviruses. The technical difficulties that we are confronted with today demand substantially more effort on the part of the Division of Biologics Standards in relation to controlling the potency, purity, and efficacy of biological preparations.

MEASLES VACCINE

Measles vaccine is now being produced, and the Division of Biologics Standards, with suitable consultants, is developing appropriate standards for the use of these vaccines. There are at least two types. One of them is a killed vaccine which at this point would seem to confer less lasting immunity than the live vaccines. On the other hand, some of the live vaccines are attended in a few persons by several days of fever, and other undesirable symptoms, which do not necessarily mean that they are dangerous in themselves. We might be able to improve them, perhaps by the concomitant administration of gamma globulin. Requests for a license, I believe, have already been received although the information submitted is incomplete.

Dr. Shannon referred to some of the problems in testing measles vaccines yesterday afternoon. A monkey, for example, that can be captured in a foreign land today will be found to be free of measles antibodies; but by the time it comes to this country and has been in more intimate contact with man than in his natural environment, we find that it has measles antibodies and therefore cannot be used for some tests of measles vaccine.

So we are forced into a program which will let us keep these monkeys in a degree of isolation that has not been necessary for other laboratory species. This is extremely expensive in terms of dollars and in terms of space.

We have made available to the Division of Biologics Standards all of the monkey space that we have on the reservation which can be made suitable for monkeys and part of the funds that are sought as an increase this year would be for contracts to procure and house monkeys suitable for measles vaccine testing. This would not be a contract let exclusively for that purpose, because it would require the participation of members of an expanded staff of Biologics Standards.

HEPATITIS INVESTIGATIONS

Within the past year, there has been some increasing interest in hepatitis virus. It probably may have been isolated in at least two different laboratories in this country.

A recent paper in the Journal of the American Medical Association representing experience of a Chicago scientist and scientists of Parke-Davis & Co. would seem to point to a prototype antihepatitis vaccine.

This last year has seen something more than 70,000 cases of hepatitis in the country, a disease which occurs in peak cycles of 7 to 8 years.

Mr. Fogarty. It is the highest ever, is it not?

Dr. Mider. I think it is the highest ever, Mr. Chairman.

Hepatitis vaccine may be in the offing.

RESPIRATORY INFECTIONS RESEARCH

The National Institute of Allergy and Infectious Diseases is already identifying organisms, mostly viruses, which are associated with respiratory infections, ranging from the sniffles to the common cold to bronchitis and pneumonia. They are actively examining the possibility of producing vaccines which may effectively prevent at least a proportion of these illnesses in human beings.

So the Division of Biologics Standards is facing a critical point in their development with the need for policing every biological that has its come along, and is still used in medicine, and the addition within the next few months, or several years of a vastly expanded responsibility.

Mr. Fogarty. Thank you, Dr. Mider.

PROGRESS OF DIVISION OF BIOLOGICS STANDARDS

I remember, I guess it was 5 or 6 years ago, Dr. Shannon, you made quite a plea for doing something in this area.

Dr. Shannon. Yes, sir.

Mr. Fogarty. This was the forgotten area of research in those days. We were falling behind in this area compared to the other Institutes. Is that not right?

Dr. Shannon. Yes, Mr. Fogarty.

Mr. Fogarty. Do you still feel today as you did then about the necessity of going ahead in this area?

Dr. Shannon. Mr. Fogarty, everything that we felt was necessary 4 or 5 years ago has come to pass—and more. I would say that today the outlook for the future is considerably more comfortable than it was 4 or 5 years ago when we first started to push this program. Now this laboratory, since its revitalization beginning 4 or 5 years ago, is playing a very active and very effective role in the development of new vaccines for the Nation.

Incidentally, it is also placing itself in a very strong position to regulate production.

But, we are still short of personnel.

PHYSICAL PLANT

Mr. Fogarty. Is your building big enough?

Dr. Shannon. No, sir. We have in the construction account funds for planning an expansion. We cannot take care of future needs within the space that we have at the present time. We have stripped some of the Institutes of space required for monkeys, and we can use certain of the farm facilities, but the type of monkey facilities that we require for the future must be in very close proximity to the laboratories which utilize these animals.

This is a very critical need. I think if the funds are granted for construction planning, we will push this as fast as we possibly can and, if necessary, we will reassign space so that this very important regulatory function will not suffer.

I think this is something we cannot let ride, regardless of what we should like to do in the other areas.

Mr. Fogarty. It has been cut back $3 million for 1962.

Dr. Shannon. There was no cut in "Biologics standards."

Dr. Mider. That is right; there is no cut.

Dr. Shannon. There was no substantial cut in "Biologics standards."

DESIRABILITY OF APPROPRIATION STRUCTURE REALINEMENT

Mr. Fogarty. If this is so important, why should it not stand out on its own and be a separate appropriation item? I think it is important enough, from what you have said over the past 4 or 5 years, to have this as a separate item.

Dr. Shannon. It could be so presented.

Mr. Fogarty. Well, what is your feeling on it? Do you think it would be better or not?

Dr. **Shannon.** It is a question of the complexity of the budget structure. My personal belief is that it should be separately presented even though it makes a complex budget, because I think that a regulatory activity of this sort probably should be given separate consideration.

Mr. **Fogarty.** I should think it would simplify it.

Dr. **Shannon.** Rather than combining it with such complex things as research, training, and the like.

Mr. **Fogarty.** I would think that would help to simplify the budget.

Dr. **Shannon.** I think they should be separated.

Mr. **Fogarty.** The mission and basic responsibility in this area are much different than the other activities covered by this appropriation.

Dr. **Shannon.** Completely different, sir.

Mr. **Fogarty.** Well, suppose you supply for us the language that would separate this.

Dr. **Shannon.** We shall be glad to do that, sir.

SEIZURE OF OUT-OF-DATE BLOOD

Mr. **Fogarty.** Did you people have anything to do with seizing some blood a few weeks ago?

Dr. **Mider.** Yes, sir, Mr. Chairman.

Mr. **Fogarty.** Some of it got into Rhode Island. Who knows this story? Can you tell us how this happened and how you took care of it?

Dr. **Mider.** I can give you the details.

Mr. **Fogarty.** It received a lot of publicity in my area. It scared a lot of people.

Dr. **Mider.** The Division of Biologics Standards was informed that a group of people in New York representing an outfit that distributed blood was changing the labels on the blood. There was an extensive investigation by members of the staff of the Division of Biologics Standards with the U.S. attorney for New York, and an 80-count indictment was recently returned by a grand jury in New York City.

The basic problem was one of updating the blood. Blood is only good for 21 days, under the law. The expiration date was increased. I understand that in certain cases the label, as to the type of blood or its subtype, may have been changed.

Mr. **Fogarty.** They were making a lot of money out of this operation, were they not?

Dr. **Mider.** I do not know, sir.

Mr. **Fogarty.** Did any deaths occur, because of this, that you know of?

Dr. **Mider.** Not that we know of, Mr. Chairman.

Mr. **Fogarty.** You were able to catch up with it in time?

Dr. **Mider.** I think they are still investigating any deleterious effects that may have occurred to individual patients who were getting the blood.

GENERAL CLINICAL RESEARCH CENTERS

Mr. **Fogarty.** I see. All right; now, what about your general clinical research centers?

Dr. Hunt. We now have 40 grants for 40 centers in 38 institutions. The two institutions that have two centers are Johns Hopkins and Colorado.

The second center in each of those places is for the investigation of diseases of children, who cannot adequately be taken care of in an adult ward.

Mr. Fogarty. What do you mean by that? These are general clinical research centers.

Dr. Hunt. The general clinical research centers can take care of children down to a certain age limit. It depends on the institution whether they feel they can go to the age of 14 or 12 or 10, or maybe below that, depending on their individual circumstances.

But in no case has a group felt that they could, within the same group of beds, take care of very young infants and young children.

SPACE RENOVATION FOR CLINICAL RESEARCH CENTERS

Mr. Fogarty. Did you have to build new facilities for these centers in these two instances, or were they set up in existing buildings?

Dr. Hunt. In every case, Mr. Chairman, the general clinical research centers, whether for adults or children, have been set up in existing space. We have no authority to build new buildings for this purpose. We have renovated existing space.

Mr. Fogarty. And that amounted to quite a bit in this area. The first year all the funds were spent on renovation, were they not?

Dr. Hunt. The first year of each grant has run very largely to renovation and the purchase of equipment.

Mr. Fogarty. What is this, the second year?

Dr. Hunt. The first grants were made 2 years ago.

Mr. Fogarty. Two years ago?

Dr. Hunt. Yes.

OPENING OF CENTERS AND SUBSEQUENT OPERATIONS

Mr. Fogarty. This year is when they are really getting started on operations?

Dr. Hunt. The center at the University of Washington was opened in the summer of 1960, so they have been going a year and a half.

Johns Hopkins was opened in August and others came on during that fall.

Mr. Fogarty. Well, give us a complete breakdown of all of them; where they are, and a brief explanation of what they are working on.

Dr. Hunt. Yes, sir; we have that.

Dr. Shannon. We have a report prepared.

(The requested information follows:)

Division of General Medical Sciences, General Clinical Research Centers, as of Feb. 14, 1962

State	Institution	Type of center
Alabama	Alabama, University of	Adult.
Arkansas	Arkansas, University of	Do.
California	Southern California, University of	Do.
Colorado	Colorado, University of	Adult: children, 2 centers.
Connecticut	Yale University School of Medicine	Adult.
Georgia	Emory University	Do.
	Georgia, Medical College of	Do.
Illinois	Chicago, University of	Do.
	Illinois, University of	Do.
	Northwestern University	Do.
Iowa	Iowa, State University of	Do.
Indiana	Indiana, University of	Do.
Kansas	Kansas, University of	Do.
Maryland	Johns Hopkins University	Adult: children, 2 centers.
	Maryland, University of	Adult.
Massachusetts	Harvard Medical School	Do.
	Tufts University	Do.
Missouri	Washington University (St. Louis)	Do.
	Supplemental award for children's unit	Children.
Michigan	Michigan, University of	Adult.
New Jersey	Seton Hall College of Medicine and Dentistry	Do.
New York	Albert Einstein College of Medicine	Do.
	Cornell University Medical College	Do.
	Montefiore Hospital	Do.
	New York University-Bellevue Medical Center	Do.
	Supplemental award for children's unit	Children.
	Rochester, University of	Adult.
North Carolina	Duke University	Adult-children.
	North Carolina, University of	Adult.
Ohio	Cincinnati, University of	Do.
	Ohio State University Research Foundation	Do.
Oklahoma	Oklahoma, University of (Medical Center)	Do.
Pennsylvania	Pennsylvania, University of	Do.
	Pittsburgh, University of	Do.
Tennessee	Vanderbilt University	Do.
Virginia	Virginia, Medical College of	Do.
Washington	Washington, University of (Seattle)	Do.
Wisconsin	Marquette University	Do.
District of Columbia	Georgetown University Hospital	Do.
Puerto Rico	Puerto Rico, University of	Do.

Special Report: Clinical Research Centers Program

BACKGROUND

Clinical studies of man and his diseases require very careful control of the patient, his diet, the medicines or other therapy administered to him, and the tests carried out in his regard. These conditions in turn demand a complex of interrelated activities and personnel embracing nursing care, diet kitchens, laboratories, specialized equipment, and treatment rooms.

In June 1959 the Senate Committee on Appropriations expressed its belief that there was an inadequate number of such clinical research facilities, in part because of the high costs of such activities, and recommended that special research centers be established throughout the country to help improve and intensify the national level of clinical studies into man's diseases and into fundamental biological conditions and problems.

A program was established by the National Institutes of Health in the fall of 1959 and assigned to the Division of General Medical Sciences for administration. In fiscal year 1961 several of the Institutes were authorized to establish centers for clinical research in cancer, heart disease, and other specific disease areas. The center program of DGMS, by contrast, is aimed toward providing facilities for research in a wide range of diseases and basic scientific problems. Research studies in numerous areas of preclinical or clinical sciences are conducted with patients under the DGMS program.

This report is intended to provide a review of developments in the general program over the past 2 years and to summarize developments in the programs of the Institutes.

GENERAL CLINICAL RESEARCH CENTERS

Funds for the establishment of the centers are provided through the grant mechanisms of NIH. Grants may be made to medical schools, research hospitals, or other appropriate medical institutions which constitute a resource for carrying out, in connection with human patients, well-designed studies in any preclinical or clinical science. For administration of the center, the sponsoring institution appoints a director and an interdepartmental supervisory committee. The supervisory committee is concerned with the merit of proposed research in the center, admission policies, potential ethical problems, and an overview of the center operation. Qualifications for grants are based primarily on the potential research productivity of the applying institution, the quality of the proposed physical facility, and the soundness of the administration to be employed in directing the center. To help insure adequate planning and stability. grants awarded for centers usually involve long-term commitments. Applications for grants are reviewed at two levels: first by a committee of consultants, and then by the National Advisory Health Council which makes its recommendations to the Surgeon General, Public Health Service.

The grants are made for the support of the basic physical resources and services essential to the conduct of a broad program of research, such as renovation of the necessary space, equipment, costs of the care of research patients (including specialized nursing, metabolic diet kitchens, and other services), supporting laboratories, and staff salaries. The grants do not provide funds for actual research projects, support for which can be obtained through other NIH research grant mechanisms or from other Federal or non-Federal sources.

ORGANIZATION OF A GENERAL CENTER

A general clinical research center is a resource within a medical institution, with the purpose of enhancing the quality and quantity of clinical investigations. It is a discrete, physical unit or research ward of about 8 to 30 beds in a hospital, apart from the general care wards, with a stable, well-trained nursing and dietetic staff to provide precise control and observation with directly supporting specialized laboratory facilities.

A typical center could consist of the following:

Bedrooms and bathrooms.
Treatment rooms.
Study rooms (for observing patients under various conditions).
Metabolic diet kitchen.
Dietitian's office.
Rooms for storing specimens.
Patients' lounge.
Space for storing linen and other similar items.
Room for keeping drugs.
Nurses' station.
Conference room.
Room for water de-ionizing equipment.
Central laboratory.
Isotope laboratory.
Biochemistry laboratory.

Laboratories.—The core laboratories, which are physically and functionally a part of the center, are utilized only for research service related to the patients of the center. They are contiguous with the bed portion of the unit except under rare, well-justified circumstances. The purpose of these laboratories is (*a*) to provide service to a considerable number of investigators in relation to their research service needs for center patients; (*b*) to perform the type of precise or experimental determinations that are not feasible for the hospital central service laboratories; and (*c*) to work primarily and directly with either center patients or with specimens from these patients. Animal research laboratories are not considered to be core laboratories. Equipment purchased for core laboratories remains within the laboratories or other areas of the center.

Nursing.—The entire nursing staff of a general center is assigned exclusively to the care of center patients. (In some centers the nursing staffs are given special training in clinical research activities.) Nurses who are not members of the center staff are not assigned to care for center patients except in the event of emergencies; and center staff nurses are not assigned to patients outside the center.

ADVANTAGES OF A GENERAL CENTER

In such a center, research scientists from many departments of an institution carry on investigations in a wide range of diseases and basic scientific problems. The advantages to medicine and biomedical research include not only the intensification and improvement per se of clinical research but also the opportunities toward these ends for integrated and coordinated efforts at the clinical level between scientists representing different medical and biological disciplines and levels of interest. In a field such as tissue and organ transplantations, for example, scientists in basic disciplines such as physiology, biochemistry, and immunology can work closely with scientists in clinical sciences, such as dermatology, surgery, and internal medicine. Likewise the field of pediatrics, for another example, can gain coordinated attention from geneticists and embryologists in the basic disciplines and from obstetricians, orthopedists, psychologists, and others in the clinical disciplines. The advantages of such interrelated studies apply with equal meaning to many other broad areas of biomedical interest, such as aging, and to many diseases, such as those involving metabolic, neurological, and congenital failures.

The benefits of a general center can be summarized as (1) providing the opportunity for meritorious clinical investigation in any or all preclinical and clinical sciences; (2) creating a cohesive force for clinical investigation in which all departments and a variety of competent and qualified investigators may participate; (3) encouraging better integrated interdisciplinary research; (4) providing opportunities for catalysis of research ideas among different investigators; (5) offering basic scientists maximum potential for clinical research; (6) offering research opportunities for those departments of a medical school not yet well established in research; and (7) affording a model of excellence for clinical research and clinical research training within an appropriate institution.

CHILDREN'S CENTERS

In line with the broader and more intense interests of the biomedical research community in children's diseases, the general clinical research centers program is providing facilities for the study of children's disorders as well as for diseases and biological conditions in adults.

Among the grants made under the general center program thus far several have been for the establishment of children's centers.

The purpose of the children's centers is to facilitate and stimulate research into a broad spectrum of conditions and diseases, of a metabolic, psychological, neurological, or congenital nature, often found in young children, and in this regard to aid and encourage coordinated work among scientists of different fields of primary interest, such as genetics and surgery, as well, of course, as the field of pediatrics itself. For this reason, the facilities of a children's center usually are available to members of other medical school departments, such as biochemistry, medicine, ophthalmology and psychiatry, as well as pediatrics, although the program director or assistant program director of the center will be a member of the Department of Pediatrics.

Aside from serving the purpose of cross-fertilization among the medical and biological disciplines, and seeking to improve the health of children themselves, this approach recognizes the fact that increased knowledge about disorders in children often can contribute directly to improved knowledge about diseases in adults.

Under the general center program, the concept of, and policies for, children's centers are the same as those of adult centers. Obvious and necessary differences do exist in management and staffing as dictated by the requirements of caring for young children, who frequently need more attention and more careful attention than adults. For example, nurses with special pediatrics training are required in children's centers, along with special facilities for recreation, extra safeguards and procedures with regard to tasks such as collecting specimens in metabolic studies, and occasionally special equipment to control temperature and humidity.

In institutions which also have adult centers, certain facilities may be shared by both units, such as metabolic kitchens, etc.

ADMINISTRATION OF THE GENERAL CENTER PROGRAM

Following the assignment to the Division of General Medical Sciences of the general clinical research center program in 1959, a section was established in the Research Grants Branch of the Division to manage general center grants. In the summer of 1961, in recognition of the growth of the program and its broadening importance to the biomedical research efforts of the Nation, the section was elevated to the status of a branch in the Division with the chief of the program answerable to the Chief of the Division.

The program is administered by the General Clinical Research Centers Branch of the Division of General Medical Sciences. The Branch has the responsibilities of interpreting its programs to applicants, grantees, and to the general public; collaborating with other elements of the National Institutes of Health (such as the Division of Research Grants, the review committees of which are made up of non-Federal consultants expert in their various fields) in conducting the primary review of each general center application, which includes a visit to the applying institution; collaborating with the National Advisory Health Council; negotiation of awards; and maintaining close liaison with grantees in matters of policy and administration of centers.

BUDGET OF THE GENERAL CENTERS PROGRAM

Following the inception of the centers program in fiscal year 1960 with a $3 million appropriation, the Congress appropriated in fiscal year 1961 $5 million directly to the Division of General Medical Sciences and $3 million to the six Institutes, a total of $8 million, for the continuing support of the general clinical research centers program. To help meet the growing demand for the establishment of these complex clinical research centers and to provide for a broader spectrum and intensification of research, the Congress appropriated $27,500,000 in fiscal year 1962. A total of $33,500,000 is requested in 1963 in order to provide for the continuation costs of centers established through 1962 and to fulfill the even greater anticipated demand for such facilities in 1963.

The $11 million appropriated during the first 2 years (fiscal years 1960–61) was used to develop 32 general clinical research centers in 31 institutions. Thus far in fiscal year 1962 (as of February 1962), awards have been made for the establishment of eight additional centers.

Thus, 40 grants for general clinical research centers have been awarded to 38 institutions. These 40 centers are distributed among 25 States, the District of Columbia, and Puerto Rico. Two institutions, Johns Hopkins University and the University of Colorado, have received two awards, one for a general adult facility, and the other for a general children's unit. New York University and Washington University have received supplemental awards for children's units which are an integral part of their general centers. A large number of additional applications are expected to be approved and awarded during the latter part of fiscal year 1962.

It is estimated that in addition to the general clinical research centers already established, many additional medical schools and other research institutions in the United States are carrying on a sufficient amount and quality of research to justify their expansion into the kind and extent of clinical research that would warrant establishment and support of additional general clinical research centers. Some of these institutions will need new construction funds before their space requirements will permit them to participate in the centers program. In these instances, coordination at the NIH between the health research facilities and the clinical research centers program is useful to the applicant institutions in overcoming problems of new construction necessary for the establishment of general clinical research centers.

PROGRAM PLANS IN FISCAL YEAR 1962

In addition to the eight new centers and five supplements recently awarded in January from fiscal year 1962 funds, a number of new centers are expected to be approved later this fiscal year. These approvals will expand the number of institutions whose ability to create ideas and perform the precise observations, controls, and techniques on fundamental scientific problems and disease entities will have been made possible through the general centers program. Research in the centers covers the broadest possible spectrum of clinical research, ranging from investigation of disease entities (such as cancer, heart, arthritis, and others) and fields such as aging and transplantation to the investigation of normal physiological functions. Examples of some specific research projects include: (1) pyrimidine and purine metabolism, (2) renal failure, (3) dopamine and related drug responsiveness in congestive heart failure, (4) chemotherapy in acute leukemia, (5) studies in epilepsy, (6) studies in medical genetics, (7) studies in bone healing, (8) studies of pancreatic function, (9) infantile eczema, (10) the development of immune mechanism, (11) ochronotic arthritis, (12) study of the intravascular invasion of cancer, and (13) a study of metabolism in the aged.

PROGRAM PLANS IN FISCAL YEAR 1963

Funds requested for fiscal year 1963 will provide an increase of $6,500,000 over the $27 million available for obligation in 1962. This $33,500,000 will permit the award of grants for the establishment of approximately 20 additional general clinical research centers at institutions demonstrating their potential for performing meritorious research, plus continuation of those centers previously established. It is anticipated that in 1963, requests for the establishment of much needed centers for children, or expansion of existing centers to accommodate children, will begin to be received in greater number.

STATUS OF THE GENERAL CENTER PROGRAM

The purpose of this section of the report is to summarize the progress made by general centers that have been or are being established. In many respects this progress necessarily is related to the length of time each grantee institution has had its award, in consideration of the time-consuming tasks of renovating space, purchasing equipment, hiring staffs, et cetera. Most of the centers established as the result of awards in May 1960 have considerable research activities to report, while those awarded since that time are in various stages of organization.

The following list of all grants made under the general center program thus far is subdivided in terms of the approximate date on which the awards were made. Following the list are more complete reports on the status of research activities in those centers which have been established for the longest period.

GENERAL CENTER AWARDS MADE IN MAY 1960

Institution	Principal investigator	Program director	Amount of 1st year's award
University of Southern California School of Medicine, Los Angeles, Calif. Center opened April 1961.	Clayton Loosli, M.D.	Don Nelson, M.D.	$321,493
Emory University School of Medicine, Atlanta, Ga. Center opened January 1961.	Arthur P. Richardson, M.D.	E. Garland Herndon, Jr., M.D.	396,179
Johns Hopkins University, Baltimore, Md. Center opened August 1960.	Thomas Turner, M.D.	W. Gordon Walker, M.D.	379,054
University of Michigan Medical School, Ann Arbor, Mich. Center not yet open.	William N. Hubbard, Jr., M.D.	Arthur B. French, M.D.	357,236
Washington University School of Medicine, St. Louis, Mo. Center opened October 1960.	David Kipnis, M.D.	David Kipnis, M.D.	338,780
New York University, Bellevue Medical Center, New York, N.Y. Center opened October 1960.	John H. Mulholland, M.D.	Currier McEwen, M.D.	439,997
University of Pennsylvania School of Medicine, Philadelphia, Pa. Center opened November 1960.	Francis Wood, M.D.	L. W. Bluemle, Jr., M.D.	420,421
University of Washington School of Medicine, Seattle, Wash. Center opened July 1960.	George N. Aagaard, M.D.	Wade Volwiler, M.D.	321,248

GENERAL CENTER AWARDS MADE IN OCTOBER 1960

Institution	Principal investigator	Program director	Amount of 1st year's award
University of Alabama Medical Center, Birmingham, Ala. Center not yet open.	Walter B. Frommeyer, M.D.	S. Richardson Hill, M.D.	$352,037
Yale University School of Medicine, New Haven, Conn. Center opened April 1961.	Paul B. Beeson, M.D.	J. W. Hollingsworth, M.D.	291,105
University of Maryland School of Medicine, Baltimore, Md. Center not yet open.	Theodore E. Woodward, M.D.	Thomas E. Connor, M.D.	189,750
Harvard Medical School, Peter Bent Brigham Hospital, Boston, Mass. Center opened October 1961.	George W. Thorn, M.D.	Warren E. C. Wacker, M.D.	662,033
Seton Hall College of Medicine and Dentistry, Jersey City, N.J. Center not yet open.	Harold Jeghers, M.D.	Philip H. Henneman, M.D.	395,083
Cornell University Medical College, New York, N.Y. Center not yet open.	John E. Deitrick, M.D.	E. Lovell Becker, M.D.	650,607
The University of Rochester School of Medicine and Dentistry, Rochester, N.Y. Center opened January 1961.	Donald G. Anderson, M.D.	Christine Waterhouse, M.D.	244,696
Duke University Medical Center, Durham, N.C. Center opened December 1960.	James B. Sidbury, Jr., M.D.	James B. Sidbury, Jr., M.D.	288,100
University of North Carolina School of Medicine, Chapel Hill, N.C. Center not yet open.	W. R. Berryhill, M.D.	Walter Hollander, Jr., M.D.	287,884
The Ohio State University, College of Medicine, Columbus, Ohio. Center opened March 1961.	George J. Hamwi, M.D.	George J. Hamwi, M.D.	279,325
Vanderbilt University School of Medicine, Nashville, Tenn. Center opened March 1961.	Elliot V. Newman, M.D.	Elliot V. Newman, M.D.	456,964

GENERAL CENTER AWARDS MADE IN SEPTEMBER 1961

University of Arkansas Medical Center, Little Rock, Ark. Center opened November 1961.	Richard V. Ebert, M.D.	James C. Melby, M.D.	$200,000
University of Colorado School of Medicine, Denver, Colo. Center not yet open.	Robert J. Glaser, M.D.	W. Dalton Jenkins, M.D.	260,000
Georgetown University School of Medicine, Washington, D.C. Center not yet open.	Hugh H. Hussey, M.D.	Geo. E. Schreiner, M.D.	300,000
Medical College of Georgia, Augusta, Ga. Center not yet open.	Wayne V. Greenberg, M.D.	Wayne V. Greenberg, M.D.	250,000
Northwestern University Medical School, Chicago, Ill. Center opened January 1962.	Richard Young, M.D.	Francesco del Greco, M.D.	250,000
University of Chicago School of Medicine, Chicago, Ill. Center opened August 1961.	H. Stanley Bennett, M.D.	Richard L. Landau, M.D.	452,416
State University of Iowa, College of Medicine, Iowa City, Iowa. Center not yet open.	Robert C. Hickey, M.D.	Robert Hodges, M.D. (Acting).	140,000
Johns Hopkins University School of Medicine, Baltimore, Md. (children's unit). Center not yet open.	Thomas B. Turner, M.D.	Barton Childs, M.D.	100,000
Tufts-New England Medical Center, Boston, Mass. Center not yet open.	Edwin B. Astwood, Ph. D., M.D.	Edwin B. Astwood, Ph. D., M.D.	300,000
Albert Einstein College of Medicine of Yeshiva University, New York, N.Y. Center not yet open.	Howard A. Eder, M.D.	Quentin Deming, M.D.	390,000

GENERAL CENTER AWARDS MADE IN SEPTEMBER 1961—Continued

Institution	Principal investigator	Program director	Amount of 1st year's award
Montefiore Hospital, New York, N.Y. Center opened December 1961.	Martin Cherkasky, M.D	Leon Hellman, M.D	$600,000
University of Pittsburgh School of Medicine, Pittsburgh, Pa. Center not yet open.	Jack D. Myers, M.D	Jack D. Myers, M.D	450,000
Marquette University School of Medicine, Milwaukee, Wis. Center not yet open.	William W. Engstrom, M.D.	Edward J. Lennon, M.D	200,000

GENERAL CENTER AWARDS MADE IN JANUARY 1962

University of Colorado Medical Center, Denver, Colo. (children's unit). Center not yet open.	C. Henry Kempe, M.D	Donough O'Brien, M.D	$150,000
University of Illinois College of Medicine, Chicago, Ill. Center not yet open.	Harry F. Dowling, M.D	Malcolm F. Stanley, M.D	450,000
Indiana University School of Medicine, Indianapolis, Ind. Center not yet open.	Wm. P. Deiss, M.D	Wm. P. Deiss, M.D	450,000
University of Kansas School of Medicine, Kansas City, Kans. Center not yet open.	C. Arden Miller, M.D	Robert E. Bolinger	400,000
University of Cincinnati Medical College, Cincinnati, Ohio. Center not yet open.	Harvey C. Knowles, Jr., M.D.	Harvey C. Knowles, Jr., M.D.	150,000
University of Oklahoma Medical Center, Oklahoma City, Okla. Center not yet open.	Harris D. Riley, Jr., M.D. M.D.	Henry Neil Kirkman, M.D	350,000
Medical College of Virginia, Richmond, Va. Center not yet open.	Solomon Papper, M.D	Solomon Papper, M.D	250,000
University of Puerto Rico School of Medicine, San Juan, P.R. Center not yet open.	Jose R. Vivas, M.D	A. A. Cintron Rivera, M.D	500,000

RESEARCH ACTIVITIES OF CERTAIN GENERAL CENTERS

University of Southern California School of Medicine, Los Angeles: This center was opened in April 1961 with 10 beds.

As of the end of calendar year 1961, 82 different patients had been admitted in a total of 1,393 patient-days.

As of December 1961, 8 months since the center was opened, a total of 15 research projects had been initiated. As an example, one study, in the field of biochemistry and nutrition, is concerned with the transport of iron into cells both from plasma and tissue fluid and during intestinal absorption. This work could relate to the treatment of abnormalities in iron metabolism.

Another study is pursuing more comprehensive knowledge of the evolution of cancer of the thyroid gland.

Other projects include studies of drugs and other factors which can reduce the excitability of the heart; investigations to produce more information on the peripheral vascular systems; studies of hemophilia; studies of cancer chemotherapy; studies of lipid metabolism in congestive heart failure; investigations into the uses of isotopic magnesium in basic metabolic studies of arthritis, heart disease and diabetes, and others.

Emory University School of Medicine: The general clinical research center at Emory University was opened in January 1961 with 10 beds. (Plans recently have been completed for the addition of 6 beds for a total of 16.)

As of the end of calendar year 1961, a total of 82 different patients had been admitted for research studies in a total of 2,150 patient-days. A total of 20 separate research projects had been initiated.

These projects include studies of the metabolism of a number of chemical substances, such as amino acids, steroids, minerals, salts, and new drugs, in relation to vairous diseases and health considerations. These include cirrhosis of the liver, collagen studies, muscular dystrophy, kidney function, activities and diseases of the thyroid and adrenal glands; congestive heart disease; and Wilson's disease.

The center also is being used for studies of the effects of psychic trauma on acute porphyria, and studies of steroid therapy on the function of the pituitary and adrenal glands.

In connection with findings thus far from the work at the Emory center, three abstracts have been prepared and submitted to the Southeastern Conference for Clinical Investigation. These are—

"Saluretic Effect of Dopamine in Patients With Congestive Heart Failure," by Drs. Robert H. McConald, Jr., Leon I. Goldberg, and Elbert P. Tuttle, Jr.

"Demonstration of Hepatic Uptake Defect in Gilbert's Disease," by Drs. John Galambos and John R. McLaren.

"Effect of Liver Injury on Incorporation of S–3504 Into Serum Protein," by Drs. John Galambos and James L. Achord.

The following abstract was submitted to the Southeastern Surgical Congress:

"Hyperchloremic Acidosis and Osteomalacia Related to Ureterosigmoidostomy," by Drs. James H. Christy, E. Garland Herndon, Jr., and Sam A. Wilkins, Jr.

Johns Hopkins University, Baltimore, Md.: The Johns Hopkins center was opened in August 1960 with 21 beds.

As o fthe end of December 1961, a total of 354 different patients had been admitted for studies in a total of 4,811 patient-days. A total of 60 research projects had been undertaken in the center.

These projects are in the fields of endocrinology, radiology, metabolism, cardiology, gastroenterology, hematology, surgery, physiology, dermatology, genetics, urology, pharmacology, and neurology.

They include studies of Sjogren's syndrome (a drying of the mucous membranes), iodine uptake of the thyroid gland, muscular dystrophy, the mechanism of renal excretion of protein, effects of gluten free diets, body composition of patients on long-term steroid therapy, cancer chemotherapy, magnesium balance, systemic mast cell disease, hypertension, coronary artery disease, chemotherapy of neoplastic diseases, and epilepsy.

Papers published by investigators of the center include the following:

Criley, J. M., and Ross, R. S.: "Mitral Valve Function in Man." Presented at the 34th Scientific Session, American Heart Association, to be published in Circulation.

Prokipchuk, E. J., Bayless, I. M., Iber, F. L., and Hendrix, T. R.: "Xylose Absorption, Distribution, and Urinary Excretion in Cirrhosis." "Clinical Research" (in press), to be presented at the eastern section meeting of the American Federation for Clinical Research, January 12, 1962.

Ross, R. S., Criley, J. M., and Morgan, R. H.: "Cineangiocardiography in Mitral Valve Disease." "Transactions of the American Association of Physicians." (In press.)

Stevens, M. B., and Knowles, B. B.: "The Significance of Urinary Gamma Globulin in Lupus Nephritis." "Arthritis and Rheumatism," volume 4, page 443, August 1961.

Washington University School of Medicine, St. Louis: This center opened in October 1960 with 15 beds.

As of the end of the calendar year 233 different patients had been admitted in a total of 4,410 patient-days. A total of 32 research projects had been initiated.

These projects include studies of the human growth hormone. Four patients with acromegaly, seven with pituitary dwarfism and several normal control patients are being studied with respect to their response to the growth hormone. Detailed information as to the metabolism of the human growth hormone in normal individuals as well as those with abnormalities of pituitary secretion have been obtained.

The subjects of other research studies include overactivity of the parathyroid glands, function of the cortex of the adrenal glands, pathogenetic mechanisms in juvenile and adult diabetics, immunology in connection with leukemia, ovarian metabolism, and kidney function.

In another study, additional information has been found on the protein transferrin which serves to transport iron in the bloodstream. One investigator is making progress in determining the production, distribution, and turnover of transferrin.

Among the papers published as the result of work in the center are the following:

Awai, M., and Brown, E. B.: "Studies of the Metabolism of Human Transferrin." (Abstract of paper presented at the meeting of the Central Society for Clinical Research, Chicago, Ill., October 1961.) (J. Lab. Clin. Med., vol. 58, p. 707, November 1961.)

Kipnis, D. M., Riddick, F. A., Jr., Williamson, J., and Lacy, P.: "Demonstration That Hormonally Determined Serum Inhibitors of Insulin Action on Skeletal Muscle Are Ineffective on Adipose Tissue." (Abstract of paper presented at the meeting of the Central Society for Clinical Research, Chicago, Ill., October 1961.) (J. Lab. Clin. Med., vol. 58, p. 836, November 1961.)

Parker, M. L., Utiger, R. D., and Daughaday, W. H.: "Studies on Human Growth Hormone—II. The Physiological Disposition and Metabolic Fate of Human Growth Hormone in Man." (Accepted for publication in the J. Clin. Invest., February 1962.)

Riddick, F. A., Jr., and Kipnis, D. M.: "Islet Cell Carcinoma and Cushing's Syndrome. Report of a Case Showing a Striking Remission With Subsequent Relapse." (In press.)

Riddick, F. A., Jr., Reisler, D., and Kipnis, D. M.: "Effect of Growth Hormone, Hydrocortisone and Alloxan Diabetes on the Sugar Transport System in Striated Muscle." (Accepted for publication in Diabetes, 1962.)

Riddick, F. A., Jr., and Reiss, E.: "Hyperparathyroidism: Analysis of Recent Experiences, Clinical Spectrum and Diagnostic Tests." (Accepted for publication in the Ann. Intern. Med., February 1962.)

Utiger, R. D., Parker, M. L., and Daughaday, W. H.: "Studies on Human Growth Hormone—I. A Radioimmunoassay for Human Growth Hormone." (Accepted for publication in the J. Clin. Invest., February 1962.)

New York University, Bellevue Medical Center: The general clinical research center at this institution was opened in October 1960 in a temporary unit with 8 beds; a permanent unit of 14 beds was opened in December 1961.

As of the end of 1961, approximately 100 different patients had been admitted to the center in a total of 915 patient-days. A total of 27 clinical research projects had been initiated.

These projects include one on burns and efforts to develop new forms of therapy. From January through June 1961, five burned patients were admitted to the general clinical research center for study. One patient was suffering burn injuries to his lungs. Two others suffered moderately severe third-degree burns. An additional two patients had severe third-degree burns over more than 50 percent of their body surfaces. Out of the studies of these patients developed additional information on the efficacy of penicillin as a single antibiotic and the use of the hypothermia mattress as a means of controlling temperature in burns.

Other projects at the center include studies of the effects of human growth hormone injected locally at the site of chronic indolent ulcers, disorders of potassium excretion, kidney diseases, hypertension, lipid metabolism, total bile and pancreatic juice secretion in certain patients, the surgical interruption of portions of the sympathetic nervous pathways to relieve pain in the hip and knee, rheumatoid lung disease, rheumatoid arthritis, the effects of metabolic defects in vitamin D-resistant rickets.

University of Pennsylvania School of Medicine, Philadelphia: A temporary clinical research center of 5 beds was opened at the University of Pennsylvania in November 1960 and a permanent unit of 10 beds will be opened this spring.

As of the last of December 1961, a total of 115 different research patients had been admitted to the center in a total of 1,505 patient-days. A total of 22 research projects had been initiated.

Among these projects is an extensive study of a family in which the parents are mentally normal but whose six children demonstrate varying degrees of retardation and bizarre behavioral development. Using a technique developed at the university for analyzing chromosomes, investigators of the center found that four of the children have a fusion of two of their chromosomes. This condition also was found in the mother's cells but not in the cells of the maternal grandmother. A fifth child has normal chromosomes and the sixth has an extra chromosome and the physical stigmata associated with mongolism. The investigators believe the chromosome anomalies probably are due to metabolic errors and are seeking to determine the exact causes. The work has the potential for offering a new insight into metabolic disturbances associated with mental retardation and may aid in the development of diagnostic and therapeutic measures to prevent or reduce such retardation.

Other projects at the center include studies of antibody response in patients with cancer; the regulation of the volume and composition of body fluids by the kidneys and endocrine glands; porphyrin, calcium, and phosphate metabolism; the mechanism of lipemia; and improved surgical techniques in connection with disorders of the bladder.

University of Washington School of Medicine, Seattle: This center, located in the Teaching and Research Hospital of the University of Washington, was opened in July 1960 with 12 beds.

Thus far 196 different patients have been admitted to the center in a total of 2,604 patient-days. A total of 39 clinical research projects have been approved by the scientific advisory committee of the center.

Specific research projects of the center include studies of patients with chronic kidney failure. With the use of artificial kidneys three patients have been kept alive for 15 months. This is the first known instance in American medical history that such an extensive study of this type has been carried out.

In other research activities, the center is investigating the physiologic controls of pancreatic digestive secretion; studying the mechanisms of the brain's control of respiration in patients having various brain and spinal cord diseases; investigating the pathways of fat metabolism in diabetic subjects and in the extremely obese patient; studying familial inheritable diseases, with emphasis on the detection and better understanding of the mechanism of biochemical derangements; and investigating the unusual primary diseases of the bones which cause collapse and debility.

In another study the center is carrying out heart catheterization studies of special types to: (1) appraise quantitatively the actual results in the performance of the heart produced by newer operations for valvular heart disease; (2) study the need and use of specific nutrients by the heart muscle itself, such as blood fat and carbohydrate.

NATIONAL CANCER INSTITUTE

Clinical cancer research requires facilities which for the most part do not conform to the specifications established by the Congress for center grants. The principal modalities of cancer therapy are surgery, radiation, and chemotherapy. The surgical research patient requires facilities and skill peculiar to the surgical wards and operating suite. The radiological research patient is usually an outpatient or requires only domiciliary care except for the time he is undergoing actual therapy. Modern radiation therapy requires massive equipment located in heavily shielded space, usually in underground locations or in separate buildings. The chemotherapy research patient is also predominantly an outpatient, hospitalized at intervals for special care or intensive study.

For these reasons, the center grant as presently defined does little to facilitate clinical cancer research except in those unusual situations where the hospital is extremely large or is devoted exclusively to cancer so that one is justified in creating not one but several centers—usually surgical, radiological, pediatric, hematology, and adult chemotherapy.

Last year before current criteria for utilizing center grant funds were in effect, the National Cancer Institute made eight grants from center funds, totaling $5,022,803. This year, the exact number and amount of new and continuing grants qualifying for support from center funds is still to be determined but is estimated at somewhere less than $2 million. This reduction is a result of the new definitions, plus the fact that one large grant initially awarded in 1961 will not be up for renewal until 1963.

One new center grant for $500,000 has been approved by the Council this year.

NATIONAL HEART INSTITUTE

The heart program-project (center) grant—coordinated with the general National Institutes of Health program for noncategorical research centers—is a logical component of the overall approach supported by the Congress for providing a new dimension in medical research, meeting both institutional and national needs.

The mechanism is ideally suited to the conduct of heart clinical investigations of a broader and deeper range than heretofore possible. It will also implement vigorous research programs in basic biological sciences and in peripheral scientific areas which will contribute needed knowledge of fundamental import to the understanding of heart disease. These areas hold promise of unraveling many problems that have baffled scientists working solely in traditional fields. Moreover, this heart program projects mechanism will enable new opportunities for interdisciplinary, collaborative research attacks combining clinical and basic approaches of categorical and noncategorical nature upon the complex riddles of the heart and circulation in health and disease.

The heart grants provide facilities for instrument and electronic development, computing and data processing, specialized animal research facilities (germ-free animal colonies) and other specialized facilities or services for which there is a long-term support requirement and which are vital to enabling a research institution to extensify and intensify its investigation of areas critical to the optimum advancement of cardiovascular knowledge.

An example of a typical heart program-project grant shows how these grants are enabling the development of new cardiocascular research resources:

A grantee institution has developed a 10-bed research component which will increase to 20 beds in the second year. The grant is providing facilities for new intensive patient care units. Complex X-ray and other instrumentation, financed by the grant, will permit new approaches to coordinated research work between such departments as cardiology, X-ray, and surgery. Ancillary aspects of this institution's new research program will involve psychobiological, epidemiological, and basic science disciplines. The heart program-project (center) grant, therefore, is adding a whole new dimension in research to this institution.

During the current fiscal year, nine grants for heart program-project centers have been awarded. This makes a total of 27 current awards—made over the past 2 years—for heart program-project centers. This represents a solid start for this important new program.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

This Institute is providing support amounting to about $370,000 through fiscal year 1962 to establish a clinical research center at the University of Colorado Medical Center, Denver. The new center will provide for unified interdepartmental clinical research and training in the allied fields of allergy, immunology, and infectious diseases.

The prospectus for the new center points out that in allergy, particularly, a large amount of developmental research remains to be done. Clinical research often can be accomplished through studies of outpatients. A small number of patients with conditions such as generalized vaccinia, bacterial or viral pneumonia, status asthmaticus, or one of the collagen diseases can be studied intensively as inpatients. The amount of laboratory work required to produce significant increases in our understanding of these diseases is likely to be extensive. For this reason it is expected that the operation of this center will be weighted heavily in favor of the laboratory. This approach should result in an increase in significant clinical research and in coordination of clinical and research teaching.

Laboratory support for the center is already available in six departments of the University of Colorado Medical Center: Medicine, pediatrics, microbiology, pathology, pharmacology, and biochemistry. This center is assured also of the active collaboration of two Denver research laboratories located at the National Jewish Hospital and the Jewish National Home for Asthmatic Children.

NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES

During the past year NIAMD has begun support of a small number of highly specialized clinical units as resources for superior clinical research in metabolism and the rheumatic diseases. Preliminary reports indicate that these small, specialized units are fulfilling effectively a need not met by other clinical center programs. In certain institutions within which there is a major research effort in arthritis, diabetes, or other areas of this Institute's particular research concern, significant value has been visualized in the organization of discrete, highly organized nursing units or wards to provide the environment required for high-level, well-controlled clinical research.

As of the date of this report three such units are being supported by this Institute; two other applications have been approved pending availability of sufficient funds. The initial research unit in this program is one of the oldest and most distinguished metabolic research wards in the United States, ward 4 of the Massachusetts General Hospital in Boston (affiliated with Harvard University). This 10-bed unit, which had been in operation for 35 years, had been in recent years very inadequately supported, resulting in curtailment of or inability to carry out a number of important clinical research studies. Award of our NIAMD grant, therefore, far from displacing other means of support, fulfilled an urgent need and has made possible continuation of metabolic research at this outstanding institution. In the past this research unit had enabled classical observations on the pathologic physiology of hyperparathyroidism, hyperthyroidism, Cushing's syndrome, rheumatoid arthritis, and ulcerative colitis. In the future similarly important studies may be expected in these and other diseases of particular interest to this Institute. The other institutions now receiving clinical research unit support are the Robert Breck Brigham Hospital in Boston (also affiliated with Harvard University), where metabolic studies are being carried on which are particularly devoted to intensified observations in rheumatoid arthritis, and the University of West Virginia University Hospital in Morgantown, where various disorders affecting the endocrine glands are under specialized study. The NIAMD Advisory Council has approved applications for smaller metabolic units at the Presbyterian-St. Luke's Hospital in Chicago and at the University of Wisconsin.

Clinical research facilities of these specialized types and generally restricted bed capacity are expected to contribute significantly to productive integration of laboratory and clinical research studies for the improved handling of patients with metabolic and rheumatic diseases.

NATIONAL INSTITUTE OF MENTAL HEALTH

The NIMH Clinical Research Center was initiated in 1961 and a total of $500,000 was made available for the first year. Three centers were established. For fiscal year 1962, $1 million was made available by congressional authorization and these funds have already been obligated for support of four additional centers.

NIMH clinical research centers approved during fiscal year 1961

Mental Retardation Clinical Research Center, Nebraska Psychiatric Institute, University of Nebraska, Omaha, Nebr., chief investigator, Cecil Wittson, M.D.—This center, designed to provide a 10- to 18-bed research ward, supporting laboratories, offices, and examining rooms, will have a staff covering a wide range of all disciplines necessary for intensive clinical investigation of mental retardation. The full-scale exploration of mental retardation will include a clarification of causes and diagnoses and the development of more useful techniques for the prevention and treatment of this condition. The center was awarded $345,000 for the period June 1, 1961–May 31, 1962, with a recommended grant of $400,000 for the second year and $200,000 for the remaining 5 years.

Psychiatric Research Center: Studies in the psychoses, Massachusetts Mental Health Center, Boston, Mass., chief investigator, Jack R. Ewalt, M.D.—Upon completion, this 10-bed research center will provide a separate research ward, assuring a high level of control over the patients and the intensive and continuous observation of the subjects. The center will permit extensions of current research projects in psychoses, particularly depression and schizophrenia, and the development of new investigations such as further exploration of the psychological and biochemical leads in depressive disorders. The center was awarded $271,332 for the period June 1, 1961–May 31, 1962, with a recommendation for six additional grants averaging $225,919 each.

Research Center for Early Childhood Schizophrenia, Carter Hospital, Indiana University Medical Center, Indianapolis, Ind., chief investigator, Marian K. DeMyer, M.D.—Carter Hospital's Research Center is being developed for the investigation of early childhood schizophrenics, that is, those children showing signs of severe disturbances before their third birthdays. The objectives of the proposed long-term studies are to develop (1) precise and objective descriptions of the young schizophrenic's behavior in relation to people and objects; (2) determining critical preceding conditions such as medical, social, and child-bearing practices producing the clinical symptoms; and (3) developing means of motivating new, predictable behavior in the children and their parents, or treatment procedures. The studies will include a small number of hospitalized and day-care patients as well as followup studies on a number of children on an outpatient basis. $180,630 was awarded to this center for the period June 1, 1961, to May 31, 1962, with a possible annual grant of $106,560 per year for the next 6 years.

Approved during fiscal year 1962

Psychiatric Research Center and program, Johns Hopkins Hospital, Baltimore, Md., chief investigator, Seymour S. Kety, M.D.—Housed within the Henry Phipps Clinic, this center will have facilities for approximately 80 inpatients, an extensive outpatient department for research, training, and service, offices for the full-time staff, the Phipps Library, and a lecture hall. The staff is planning a well-rounded program of psychiatric research—biological, psychological, and sociological—including both basic and clinical studies, and to train young investigators in the scientific concepts and techniques necessary for research in this area. The center was granted $202,718 for the period October 1, 1961–September 30, 1962, with a recommendation that approximately $167,950 for support be awarded for the following 6 years.

Clinical Psychiatric Research Center, State University of New York, Downstate Medical Center, Brooklyn, N.Y., chief investigator, I. Charles Kaufman, M.D.—This center will operate a 20-bed research ward as well as laboratories and other facilities for the observation of psychiatric treatment processes. The center will be organized around a core treatment and assessment program to which each patient will be exposed. Behavior during treatment will be monitored and recorded by means of a closed-circuit TV system, with a remote control analog facility automatically transmitting and recording data for computer analysis. The center will serve as the main clinical research facility for the investigators of the Department of Psychiatry of the Downstate Medical Center as well as a center for training in psychiatric research. NIMH awarded $90,000 to this center in October 1961 for its first-year support with a recommendation that $350,000 subject to negotiation, be granted annually for the following 6 years.

Psychosomatic and Psychiatric Clinical Research Center, Michael Reese Hospital and Medical Center, Chicago, Ill., Roy R. Grinker, M.D., chief investigator.—The major research focus at this center is on psychosomatic response to stress with a secondary interest in the area of ego functions. A new and separate inpatient unit is being constructed by modifying one section of the present Psychosomatic and Psychiatric Clinical Research Center, thus providing facilities for controlled hospital studies of five inpatients. NIMH awarded the center support amounting to $103,203 in October 1961 for the first year and recommended an average annual grant of $103,343 for 6 additional years.

Establishment of the Center of Alcohol Studies, Rutgers, the State University, New Brunswick, N.J., chief investigator, Selden D. Bacon, M.D.—The NIMH research grant to this facility provided for the transfer of the center from Yale University in New Haven, Conn., to Rutgers, both to pay for the actual move and to help the center become reestablished in its new location. Studies in alcoholism here will include three functions: research, training, and publication and documentation. The initial NIMH grant amounted to $222,545 to run from October 1, 1961, to September 30, 1962, $222,545 was recommended for the second year and an average grant of $141,000 per year for 5 following years.

NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS

Within the National Institute of Neurological Diseases and Blindness, the program project grant has been developed as the categorical extension of the established Clinical Research Center. These grants provide broad support of the research program as well as the clinical resources needed for this research.

These project grants involve either a multidisciplinary attack on specific neurological or sensory diseases or a disciplinary attack on a group of neurological and sensory disorders. Three cerebrovascular research centers are being established at Cornell University, University of Minnesota, and Wayne State University. Also, underway are the following: An epilepsy center at the University of Wisconsin; a neurosensory center at the State University of Iowa; a sensory disease center focusing on disorders of vision, hearing, and equilibrium at the University of Chicago; a center to study the connective tissues of the eye and connective tissue diseases at the Retina Foundation; a study of brain damage and defective brain development in children at Albert Einstein College of Medicine; a broad neurophysiological study of various neurological diseases at the

University of California; and two neurological clinical research centers at Columbia University and Albert Einstein College of Medicine.

One program was started in 1960, six programs were begun in 1961, and in 1962 there have been four additional programs started to date. All of the program projects to date are basically clinical. About 40 percent of the funds for the first year are for the support of center facilities.

This Institute now has 11 active awards totaling $2,068,297. The center facility portion of these awards have required $882,000 out of the $1 million earmarked in the 1962 budget for this purpose. Eleven additional applications requesting $3,237,326 will be considered during the next two meetings of the National Advisory Neurological Diseases and Blindness Council.

GENERAL RESEARCH SUPPORT GRANTS

Mr. Fogarty. What about your general research support grants?

Dr. Hunt. These were made for the first time within the past month to 153 institutions.

Mr. Fogarty. Will you put those institutions' names, State by State, in the record, too?

Dr. Hunt. We have those listed by State and institution.

Mr. Fogarty. This is a new program in 1962.

Dr. Hunt. Yes. This was the first year.

Mr. Fogarty. It is my understanding that these grants are financed by all of the institutes, but they are being administered by this Division.

Dr. Hunt. That is correct.

(The requested information follows:)

Special Report: General Research Support Grant Program

FOREWORD

Public Law 86–798, approved September 15, 1960, provided the Public Health Service authority for the establishment of the general research support grant program. The act reads:

> "To amend the Public Health Service Act to authorize grants-in-aid to universities, hospitals, laboratories, and other public or nonprofit institutions to strengthen their programs of research and research training in sciences related to health
>
> "*Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled*, That section 301(d) of the Public Health Service Act, as amended (42 U.S.C. 241(d), is amended by adding after the semicolon at the end thereof "and make, upon recommendation of the National Advisory Health Council, grants-in-aid to public or nonprofit universities, hospitals, laboratories, and other institutions for the general support of their research and research training programs; *Provided*, That such uniform percentage, not to exceed 15 per centum, as the Surgeon General may determine, of the amounts provided for grants for research projects for any fiscal year through the appropriations for the National Institutes of Health may be transferred from such appropriations to a separate account to be available for such research and research training program grants-in-aid for such fiscal year;".

The program has been initiated in fiscal year 1962 with an appropriation of $20 million. It is being administered by the NIH Division of General Medical Sciences.

PURPOSE

The purpose of the general research support grant program is to provide special grants to health-related research and educational institutions to aid in the development and maintenance of sound, well-balanced programs of general research and research training in medical, dental, public health, and related areas. Coupled with assurances of long-term support, these funds will enable the institutions to develop health research and research training activities in a consistent and planned manner in accordance with the overall objectives of the institution; to provide stable careers for their scientists; and to aid younger scientists.

The new grant program came about as a result of the phenomenal growth of research in medicine and biology in recent years, the increasing need to train young scientists in research techniques, and the impact of the rising level of financial support in these areas being provided by the National Institutes of Health. In the past 15 years the amount of funds available for extramural research and training under the project systems has risen from $3.5 million to over $525 million. The annual total number of research grants, nearly all of which are awarded for specific research projects, is now more than 13,000. Within single institutions, such as universities, for example, there may be more than 100 scientists working on separate NIH-supported projects.

The above facts suggested the need for making broader grants of the institutional type to the Nation's educational institutions for the purpose of assuring their continued autonomy, freedom, and ability to keep control of the character and direction of their revolving health research activities. Thus the General Research support grant programs will contribute to the financial flexibility of the institutions, and help them in meeting their twin goals of optimum development of their own total research efforts, while at the same time assuring full productivity by their individual investigators.

The program will augment and not replace the system of grants to individual scientists for the support of specific projects. Individual projects will continue to be the largest segment of the total research grant program. In this regard it is significant that many thousands of NIH research grants go to private research groups and individuals other than educational institutions.

Furthermore institutions which receive General Research support grants are eligible to apply for all other forms of support for research and research training from NIH, with the following exceptions:

1. Applications for research grants for less than $2,000 in 1 year.
2. Supplemental applications during the active year of a research grant to cover the cost of general institutional salary or fringe benefit increases during that year for persons whose salaries are paid from Public Health Service grants or awards.
3. Applications for the former students part time and postsophomore training programs.

The General Research support grant will be the mechanism through which funds will be available for these purposes. Institutions may secure non-NIH support for these and any other programs without adversely affecting the amount of their General Research support grant.

INSTITUTIONS ELIGIBLE TO APPLY

For the first year of operation, eligibility to apply for General Research support grants was limited to schools of medicine, dentistry, osteopathy, and public health.

It is expected that eligibility to receive these grants will be extended in fiscal year 1963 to those schools of nursing, schools of pharmacy, schools of veterinary medicine, hospitals and other nonprofit research organizations that are determined to be heavily engaged in research related to health.

COMPUTING THE SIZE OF EACH GRANT

The amount to be awarded to each educational institution is based on a formula which takes several factors into account, including the amount of research being carried on by the institution with non-Federal financing. The salient features of the formula, quoted from the Policy and Information statement, dated August 4, 1961 (copy attached), are as follows:

"1. Each eligible institution will receive a basic amount, to insure that it will have a minimum financial base for a research and research training program. During fiscal year 1962 this amount will be $25,000.

"2. The second factor in the formula is based upon the total health-related research expenditures of the recipient institution in its latest complete fiscal year, up to a maximum of $2 million, sponsored by Federal research grants and contracts (excluding grants, contracts, and awards for education, training, and construction). The preliminary computation of the formula will utilize figures representing 5 percent of the first $1 million of such expenditures, and 3 percent of the amount between $1 and $2 million.

"3. The third factor is based upon the total health-related research expenditures of the recipient institution in its latest complete fiscal year, up to a maximum of $2 million, sponsored by non-Federal grants, contracts, and gifts restricted for research (excluding grants, contracts, and awards for education, training, and construction). The preliminary computation of the formula will utilize figures representing 10 percent of the first $1 million of such expenditures, and 6 percent of the amount between $1 and $2 million.

"4. The sum of the amounts produced by application of the above factors will, if necessary, be increased or decreased by whatever uniform percentage is required to adjust the total amount of the awards to the total funds available for General Research support grants.

"5. For each recipient institution, an amount equal to 15 percent of the grant will be added to the grant for support of the indirect costs of research and research training."

It should be noted that the figures resulting from the application of this formula will be adjusted upward or downward to adjust the total amount of the awards to the total funds available for the program.

Awards will be on a calendar year basis, January 1 through December 31. An amount not exceeding the amount of the grant received in 1 year may be carried over to the succeeding grant year without affecting the amount of the grant in the latter year.

UTILIZATION OF GRANT FUNDS

A unique feature of the General Research support grant program is the considerable freedom recipient institutions will have in determining the particular research and/or research training purposes to which they assign the funds. It is expected that the grants will be used for four principal kinds of research and research training activity, as indicated in the policy and information statement:

"1. Support of resources; for example, the operation of central research resources, such as animal facilities, not related solely to any one specific project or program but essential to the entire health-related research activity of the institution (care should be exercised to insure that these costs are not also charged to other Public Health Service grants); the provision of ancillary research services, such as shop and instrument work.

"2. Support of personnel; especially the provision of stable salary support for staff members engaged in research and research training whose salaries would otherwise be dependent on individual research grants or similar less stable sources. Any payments of stipends to trainees should be in accordance with Public Health Service policies.

"3. Support of projects; for example, the support of promising ideas that require further exploration and development prior to more formal consideration for project support; the payment of unexpected expenses in an established project.

"4. Support of certain activities now covered by Public Health Service grants, for which support will no longer be available on an individual basis; for example, research grants for less than $2,000 in 1 year; supplemental grants during an active grant year for salary increases; grants for student part time and post-sophomore training programs."

These funds generally are subject to the policies applying to all Public Health Service grants for research and training. General Research support grants may not be used for costs of new construction, alteration, or renovation of space.

INDIRECT COSTS

Public Law 86–798 does not give the Public Health Service any expanded authority to support new types of expenditures. Thus a grant under this program may be used only for the direct costs of research and research training, except that an amount equivalent to 15 percent of the grant will be added to the grant for indirect costs.

AUDITING AND REPORTING

General Research support grants will be subject to audit verifying the institution's income and expenditures for sponsored research used in computing the grants, as well as the direct expenditures for research purposes of determining that calculations have been based on allowable direct costs.

Each grantee institution will be required to submit an annual report which should include description of the institutional benefits derived from the grant.

GRANTEE INSTITUTIONS

All of the 153 eligible institutions have been awarded grants in January 1962, as follows:

Type of school	Number of schools	Total awards
Dentistry	49	$2,025,143
Medicine	86	16,471,926
Osteopathy	6	209,054
Public health	12	1,293,877
Total	153	20,000,000

POLICY AND GENERAL INFORMATION ON GENERAL RESEARCH SUPPORT GRANTS

GENERAL RESEARCH SUPPORT GRANTS

A. Background

Public Law 86–798, approved September 15, 1960, authorizes the Surgeon General, upon recommendation of the National Advisory Health Council, to make grants "to public or nonprofit universities, hospitals, laboratories, and other institutions for the general support of their research and research training programs." Under this authority, the National Institutes of Health is initiating a program of General Research support grants in fiscal year 1962.

B. Purpose of the grants

The purpose of General Research support grants is to provide funds to eligible institutions on a continuing basis for the general support of their research and research training program in sciences related to health. Expenditures under these grants must contribute clearly and directly to the research and research training programs of the institution. It is expected that funds available though the grant will augment institutional funds available for research and research training. Within these general guides and subject to the policies applying to Public Health Service grants for research and training, except as specifically provided otherwise below, the recipients are free to determine the uses to which the funds will be put. These policies are stated in "Grant and Award Programs of the Public Health Service," (vol. I and vol. II), 1959, National Institutes of Health, Bethesda, Md.

C. Uses of grant

The unique feature of the General Research support grant is that the recipient institution has greater freedom in determining the specific uses of the funds than is the case with other kinds of Public Health Service grants. The General Research support grant may be used only for the direct costs of research and research training as defined in "Grant and Award Programs of the Public Health Service," as modified or amended. It is expected that any institutional funds formerly devoted to research or research training, which may be released by the use of the General Research support grant, will continue to be used for such direct costs. The General Research support grant may not be used for the indirect costs of research, except as specified below, nor for the costs of new construction, alteration, or renovation. An amount equivalent to 15 percent of the grant will be added to the grant for the support of the indirect costs of the research and research training carried out by the recipient institution.

It is expected that the grant will be used for four principal kinds of research and research training activity:

1. Support of resources: for example, the operation of central research resources, such as animal facilities, not related solely to any one specific project or program but essential to the entire health related research activity of the institution (care should be exercised to ensure that these costs are not also charged to other Public Health Service grants); the provision of ancillary research services, such as shopwork.

2. Support of personnel; especially the provision of stable salary support for staff members engaged in research and research training whose salaries would otherwise be dependent on individual research grants or similar less stable sources. Any payments of stipends to trainees should be in accordance with Public Health Service policies.

3. Support of projects; for example, the support of promising ideas that require further exploration and development prior to more formal consideration for project support; the payment of unexpected expenses in an established project.

4. Support of certain activities now covered by Public Health Service grants, for which support will no longer be available on an individual basis; for example, research grants for less than $2,000 in 1 year; supplemental grants during an active grant year for salary increases; grants for student part time and post-sophomore training programs.

D. Institutions eligible to apply

In fiscal year 1962 (beginning July 1, 1961) institutions which may establish eligibility to receive general research grants are schools of medicine, schools of dentistry, schools of osteopathy, and schools of public health.

It is expected that eligiblity to receive general research support grants will be extended in fiscal year 1963 to those schools of nursing, schools of pharmacy, schools of veterinary medicine, hospitals and other nonprofit research organizations that are determined to be heavily engaged in research related to health. These institutions will be requested to submit in fiscal year 1962 data which will permit (1) determination of their eligibility for a general research support grant, and (2) determination of the amount of the award to be made in fiscal year 1963.

E. The application process

Eligible institutions interested in making application for an award during fiscal year 1962 are invited to write not later than September 1, 1961, to the Chief, Division of General Medical Sciences, National Institutes of Health, Bethesda, Md., expressing their intent to apply and requesting application forms. In the initial year, applications for general research support grants should be submitted by October 1, 1961.

The formal application will require the applying institution to supply the following information to establish eligibility and to permit computation of the amount of the grant:

1. A statement outlining in broad terms the institution's plans to develop the four kinds of activities described in section C, and any others, and describing the administrative procedures that the institution will establish to determine the uses of the funds.

2. A statement of the institution's total expenditures for research financed from outside sources, by source of support, in the latest complete institutional fiscal year for which data are available. (See section F below for definitions.)

E. Computation of grant

The amount available for distribution as general research support grants will constitute "such uniform percentage, not to exceed 15 percentum, as the Surgeon General may determine, of the amounts provided for grants for research projects for any fiscal year through the appropriations for the National Institutes of Health * * *" (Public Law 86–798). During the initial year of the program, the Surgeon General has determined that an amount of approximately 5 percent of the total appropriation for regular research projects will be devoted to general research support grants.

The distribution of the available total sum among eligible institutions will be determined by a formula, the salient features of which are as follows:

1. Each eligible institution will receive a basic amount, to insure that it will have a minimum financial base for a research and research training program. During fiscal year 1962 this amount will be $25,000.

2. The second factor in the formula is based upon the total health related research expenditures of the recipient institution in its latest complete fiscal year, up to a maximum of $2 million, sponsored by Federal research grants and contracts (excluding grants, contracts, and awards for education, training, and construction). The preliminary computation of the formula will utilize figures representing 5 percent of the first $1 million of such expenditures, and 3 percent of the amount between $1 million and $2 million.

3. The third factor is based upon the total health related research expenditures of the recipient institution in its latest complete fiscal year, up to a maximum of $2 million, sponsored by non-Federal grants, contracts, and gifts restricted for research (excluding grants, contracts and awards for education, training and construction). The preliminary computation of the formula will utilize figures representing 10 percent of the first $1 million of such expenditures, and 6 percent of the amount between $1 million and $2 million.

4. The sum of the amounts produced by application of the above factors will, if necessary, be increased or decreased by whatever uniform percentage is required to adjust the total amount of the awards to the total funds available for general research support grants.

5. For each recipient institution, an amount equal to 15 percent of the grant will be added to the grant for support of the indirect costs of research and research training.

6. The maximum amount available to any institution in fiscal year 1962 will approximate $300,000.

F. Definitions of grants, contracts, and gifts

Funds that can be counted are those from "outside" sources, i.e., "sponsored" research, in the form of grants, contracts, or gifts restricted for research. The definitions are as follows:[1]

Sponsored research programs are those research activities fostered and supported by funds from outside agencies or organizations through grants, contracts and/or gifts which are "restricted for research." Such sponsored programs often are tailored to the resources and interests of the sponsoring agencies rather than the basic needs of the institutions. Grants, contracts, and gifts restricted for research include only those expenditures made in accordance with the conditions of grants and contracts which have been awarded and gifts which have been given with the express stipulation that the use of funds derived therefrom is restricted to the support of specifically designated research projects, programs or areas. This includes research grants and contracts awarded by the Federal agencies, foundations, and other nonprofit organizations, industrial firms, agencies of State and local government, and other organizations. It includes expenditures of income or expenditure of capital from gifts or endowments which the donor has restricted for research.

Funds excluded are: (1) All endowment income except that specifically restricted for research, (2) State appropriations not in the form of research grants or contracts, and (3) the Public Health Service general research support grant.

G. Eligibilty to receive other NIH support

Institutions which receive general research support grants are eligible to apply for all other forms of support for research and research training from NIH, with the following exceptions:

1. Applications for research grants for less than $2,000 in 1 year.

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[1] These definitions correspond with those developed for the annual survey of medical school finances conducted by the Liaison Committee on Medical Education which is jointly sponsored by the Council on Medical Education and Hospitals of the American Medical Association and the Association of American Medical Colleges. Medical schools should base the information supplied on the general research support grant application upon the research expenditure data supplied to the liaison committee. Similar data on research expenditures under Federal and non-Federal research grants, contracts, and gifts restricted for research must be submitted by other eligible institutions.

2. Supplemental applications during the active year of a research grant to cover the cost of general institutional salary or fringe benefit increases during that year for persons whose salaries are paid from Public Health Service grants or awards.

3. Applications for the former student part-time and post-sophomore training programs.

The general research support grant will be the mechanism through which the Public Health Service will provide funds for these purposes. Institutions may secure non-NIH support for these and any other programs, without adversely affecting the amount of their general research support grant.

H. Carryover of funds

An amount not exceeding the amount of the general research support grant received in the preceding year may be carried over to the succeeding year without affecting the amount of the grant in the succeeding year.

I. Annual reports

Each institution receiving a general research support grant will submit an annual report describing the utility of the grant in strengthening specific activities in health research and research training. The report should also contain a carefully considered assessment of the institutional functions aided by the grant funds. If specific research projects were aided from the general research support grant, the project and the responsible investigator should be identified. If a substantial sum is carried forward from one year to the next, the reason for the carryover should be explained. More detailed instructions will be issued later to institutions receiving grants.

In addition, the annual report should record the amounts spent for each of the principal kinds of research and research training activity, as outlined in section C, with identification of the total amount spent for each of the following:

Personnel.
Equipment.
Consumable supplies.
Travel.
Costs for study patients: Hospitalization costs; outpatient costs.

J. Patent provisions

Any invention first conceived and actually reduced to practice in the course of work conducted under any specific research project which the grantee institution aided through the general research support grant shall be promptly and fully reported to the Surgeon General so that the public interest may be protected.

Whether patent protection on such an invention shall be sought and how the rights in the invention, including rights under any patent issued, shall be disposed of and administered shall be determined either (*a*) by the Surgeon General, or (*b*) by the grantee institution in accordance with its own policies. (Clause (*b*) applies only in those cases where a separate formal agreement as to patent rights has been reached by the Surgeon General with the grantee institution prior to submission of the applications concerned.)

Amounts to be awarded for general research support grants to accredited schools of dentistry, medicine, osteopathy, and public health, fiscal year 1962

Grant No.	Schools	Direct costs	Indirect costs	Total
	DENTAL (49)			
	Alabama:			
GS-1	University of Alabama	$58,913	$8,837	$67,750
	California:			
GS-2	College of Physicians and Surgeons	27,823	4,173	31,996
GS-3	Loma Linda University	27,030	4,054	31,084
GS-4	University of Southern California (Los Angeles)	30,925	4,639	35,564
GS-5	University of California Medical Center (Los Angeles).	25,000	3,750	28,750
GS-6	University of California Medical Center (San Francisco).	33,793	5,069	38,862
	District of Columbia:			
GS-7	Georgetown University	39,799	5,970	45,769
GS-8	Howard University	32,119	4,818	36,937
	Georgia:			
GS-9	Emory University	42,703	6,406	49,109
	Illinois:			
GS-10	University of Illinois	69,104	10,366	79,470
GS-11	Loyola University	37,706	5,656	43,362
GS-12	Northwestern University	46,659	6,999	53,658
	Indiana:			
GS-13	Indiana University	50,473	7,571	58,044
	Iowa:			
GS-14	State University of Iowa	26,203	3,930	30,133
	Kentucky:			
GS-15	University of Kentucky	25,000	3,750	28,750
GS-16	University of Louisville	27,392	4,109	31,501
	Louisiana:			
GS-17	Loyola University	25,456	3,818	29,274
	Maryland:			
GS-18	Baltimore College of Dental Surgery	26,233	3,935	30,168
	Massachusetts:			
GS-19	Harvard School of Dental Medicine	57,423	8,614	66,037
GS-20	Tufts University	75,001	11,250	86,251
	Michigan:			
GS-21	University of Detroit	25,428	3,814	29,242
GS-22	University of Michigan	35,912	5,387	41,299
	Minnesota:			
GS-23	University of Minnesota	32,783	4,917	37,700
	Missouri:			
GS-24	University of Kansas City	33,585	5,038	38,623
GS-25	St. Louis University	29,422	4,413	33,835
GS-26	Washington University	35,636	5,345	40,981
	Nebraska:			
GS-27	The Creighton University	26,198	3,930	30,128
GS-28	University of Nebraska	26,094	3,914	30,008
	New Jersey:			
GS-29	Fairleigh Dickinson University	25,000	3,750	28,750
GS-30	Seton Hall College	29,686	4,453	34,139
	New York:			
GS-31	University of Buffalo	27,232	4,085	31,317
GS-32	Columbia University	72,263	10,840	83,103
GS-33	New York University	73,049	10,957	84,006
	North Carolina:			
GS-34	University of North Carolina	33,083	4,962	38,045
	Ohio:			
GS-35	Ohio State University	36,041	5,406	41,447
GS-36	Western Reserve University	29,049	4,357	33,406
	Oregon:			
GS-37	University of Oregon	35,983	5,398	41,381
	Pennsylvania:			
GS-38	University of Pennsylvania	35,454	5,318	40,772
GS-39	University of Pittsburgh	35,386	5,308	40,694
GS-40	Temple University	29,580	4,437	34,017
	Puerto Rico:			
GS-41	University of Puerto Rico	31,140	4,671	35,811
	Tennessee:			
GS-42	Meharry Medical College (S.D.)	26,463	3,970	30,433
GS-43	University of Tennessee	25,187	3,778	28,965
	Texas:			
GS-44	Baylor University College of Dentistry	30,068	4,510	34,578
GS-45	University of Texas	38,649	5,797	44,446
	Virginia:			
GS-46	Medical College of Virginia	27,148	4,072	31,220
	Washington:			
GS-47	University of Washington	33,843	5,077	38,920
	West Virginia:			
GS-48	West Virginia University	28,471	4,271	32,742
	Wisconsin:			
GS-49	Marquette University	28,406	4,260	32,666
	Total	1,760,994	264,149	2,025,143

Amounts to be awarded for general research support grants to accredited schools of dentistry, medicine, osteopathy, and public health, fiscal year 1962—Continued

Grant No.	Schools	Direct costs	Indirect costs	Total
	MEDICAL (86)			
	Alabama:			
GS-50	University of Alabama	$88,167	$13,225	$101,392
	Arkansas:			
GS-51	University of Arkansas	84,264	12,640	96,904
	California:			
GS-52	University of California (Los Angeles)	284,911	42,737	327,648
GS-53	University of California (San Francisco)	307,265	46,090	353,355
GS-54	Loma Linda University	160,695	24,104	184,799
GS-55	University of Southern California	169,133	25,370	194,503
GS-56	Stanford University	304,169	45,625	349,794
	Colorado:			
GS-57	University of Colorado	180,446	27,067	207,513
	Connecticut:			
GS-58	Yale University	288,357	43,253	331,610
	District of Columbia:			
GS-59	George Washington University	88,951	13,343	102,294
GS-60	Georgetown University	142,906	21,436	164,342
GS-61	Howard University	53,905	8,086	61,991
	Florida:			
GS-62	University of Florida	102,667	15,400	118,067
GS-63	University of Miami	240,554	36,083	276,637
	Georgia:			
GS-64	Emory University	144,460	21,669	166,129
GS-65	Medical College of Georgia	80,088	12,013	92,101
	Illinois:			
GS-66	Chicago Medical School	113,088	16,963	130,051
GS-67	University of Chicago	371,019	55,653	426,672
GS-68	Loyola University	50,410	7,562	57,972
GS-69	University of Illinois	216,794	32,519	249,313
GS-70	Northwestern University	211,710	31,756	243,466
	Indiana:			
GS-71	Indiana University	172,533	25,880	198,413
	Iowa:			
GS-72	State University of Iowa	162,125	24,319	186,444
	Kansas:			
GS-73	University of Kansas	138,597	20,789	159,386
	Kentucky:			
GS-74	University of Kentucky	48,111	7,217	55,328
GS-75	University of Louisville	129,011	19,352	148,363
	Louisiana:			
GS-76	Louisiana State University	89,565	13,435	103,000
GS-77	Tulane University	206,625	30,993	237,618
	Maryland:			
GS-78	Johns Hopkins University	252,418	37,863	290,281
GS-79	University of Maryland	184,231	27,635	211,866
	Massachusetts:			
GS-80	Boston University	119,162	17,874	137,036
GS-81	Harvard Medical School	256,666	38,500	295,166
GS-82	Tufts University	103,810	15,572	119,382
	Michigan:			
GS-83	University of Michigan	272,189	40,828	313,017
GS-84	Wayne State University	163,242	24,486	187,728
	Minnesota:			
GS-85	University of Minnesota	305,624	45,844	351,468
	Mississippi:			
GS-86	University of Mississippi	97,282	14,592	111,874
	Missouri:			
GS-87	University of Missouri	50,406	7,561	57,967
GS-88	St. Louis University School of Medicine	103,186	15,478	118,664
GS-89	Washington University	251,395	37,709	289,104
	Nebraska:			
GS-90	Creighton University	49,749	7,462	57,211
GS-91	University of Nebraska	67,053	10,058	77,111
	New Hampshire:			
GS-92	Dartmouth Medical College	91,690	13,753	105,443
	New Jersey:			
GS-93	Seton Hall College	105,417	15,812	121,229
	New York:			
GS-94	Albany Medical College of Union University	109,600	16,440	126,040
GS-95	University of Buffalo	250,212	37,532	287,744
GS-96	Columbia University	371,019	55,653	426,672
GS-97	Cornell University	365,591	54,839	420,430
GS-98	Albert Einstein College of Medicine	251,956	37,793	289,749
GS-99	New York Medical College	167,181	25,077	192,258
GS-100	New York University	371,019	55,653	426,672
GS-101	State University of New York (Downstate)	175,130	26,269	201,399
GS-102	State University of New York (Upstate)	102,798	15,420	118,218
GS-103	University of Rochester	319,336	47,900	367,236

Amounts to be awarded for general research support grants to accredited schools of dentistry, medicine, osteopathy, and public health, fiscal year 1962—Continued

Grant No.	Schools	Direct costs	Indirect costs	Total
	MEDICAL (86)—continued			
	North Carolina:			
GS-104	Bowman Gray School of Medicine	$116. 397	$17, 459	$133. 856
GS-105	Duke University	197. 838	29, 676	227. 514
GS-106	University of North Carolina	122, 277	18, 342	140, 619
	North Dakota:			
GS-107	University of North Dakota	37, 144	5, 573	42, 717
	Ohio:			
GS-108	University of Cincinnati	249, 623	37, 443	287. 066
GS-109	Ohio State University	150, 543	22, 582	173. 125
GS-110	Western Reserve University	286, 170	42, 925	329, 095
	Oklahoma:			
GS-111	University of Oklahoma	93, 770	14, 065	107, 835
	Oregon:			
GS-112	University of Oregon	165, 516	24, 827	190, 343
	Pennsylvania:			
GS-113	Hahnemann Medical College	113. 881	17, 082	130, 963
GS-114	Jefferson Medical College of Philadelphia	178. 051	26, 708	204, 759
GS-115	University of Pennsylvania	331. 069	49, 660	380, 729
GS-116	University of Pittsburgh	243. 362	36. 504	279, 866
GS-117	Temple University	145. 520	21, 828	167, 348
GS-118	Woman's Medical College of Pennsylvania	41, 357	6, 203	47, 560
	Puerto Rico:			
GS-119	University of Puerto Rico	75, 145	11, 272	86, 417
	South Carolina:			
GS-120	Medical College of South Carolina	71, 772	10, 766	82, 538
	South Dakota:			
GS-121	State University of South Dakota	35, 414	5, 312	40, 726
	Tennessee:			
GS-122	Meharry Medical College	45, 024	6. 754	51, 778
GS-123	University of Tennessee	145. 217	21, 783	167, 000
GS-124	Vanderbilt University	163, 761	24, 564	188, 325
	Texas:			
GS-125	Baylor University	249. 230	37, 385	286. 615
GS-126	University of Texas (Dallas)	158, 671	23. 801	182, 472
GS-127	University of Texas (Galveston)	129, 203	19, 381	148, 584
	Utah:			
GS-128	University of Utah	183, 964	27, 595	211, 559
	Vermont:			
GS-129	University of Vermont	79, 437	11, 916	91, 353
	Virginia:			
GS-130	Medical College of Virginia	165. 535	24, 830	190, 365
GS-131	University of Virginia	100, 301	15, 045	115, 346
	Washington:			
GS-132	University of Washington	273, 467	41, 020	314, 487
	West Virginia:			
GS-133	West Virginia University	37, 730	5, 659	43, 389
	Wisconsin:			
GS-134	Marquette University	102, 068	15, 310	117, 378
GS-135	University of Wisconsin	247, 069	37, 060	284, 129
	Total	14, 323, 414	2, 148, 512	16, 471, 926
	OSTEOPATHY (6)			
	California:			
GS-136	College of Osteopathic Physicians and Surgeons	$34, 290	$5, 143	$39, 433
	Illinois:			
GS-137	Chicago College of Osteopathy	26, 737	4, 011	30, 748
	Iowa:			
GS-138	College of Osteopathic Medicine and Surgery	25, 287	3, 793	29, 080
	Missouri:			
GS-139	Kansas City College of Osteopathy and Surgery	27, 810	4, 171	31, 981
GS-140	Kirksville College of Osteopathy and Surgery	42, 217	6, 333	48, 550
	Pennsylvania:			
GS-141	Philadelphia College of Osteopathy	25, 445	3, 817	29, 262
	Total	181, 786	27, 268	209, 054

Amounts to be awarded for general research support grants to accredited schools of dentistry, medicine, osteopathy, and public health, fiscal year 1962—Continued

Grant No.	Schools	Direct costs	Indirect costs	Total
	PUBLIC HEALTH (12)			
	California:			
GS-142	University of California (Berkeley)	$105,391	$15,809	$121,200
GS-143	University of California (Los Angeles)	48,937	7,341	56,278
	Connecticut:			
GS-144	Yale University	59,849	8,977	68,826
	Louisiana:			
GS-145	Tulane University	41,437	6,216	47,653
	Maryland:			
GS-146	Johns Hopkins University	135,046	20,257	155,303
	Massachusetts:			
GS-147	Harvard School of Public Health	198,315	29,747	228,062
	Michigan:			
GS-148	University of Michigan	132,064	19,810	151,874
	Minnesota:			
GS-149	University of Minnesota	71,727	10,759	82,486
	New York:			
GS-150	Columbia University	84,161	12,624	96,785
	North Carolina:			
GS-151	University of North Carolina	45,033	6,755	51,788
	Pennsylvania:			
GS-152	University of Pittsburgh	178,150	26,722	204,872
	Puerto Rico:			
GS-153	University of Puerto Rico	25,000	3,750	28,750
	Total	1,125,110	168.767	1,293,877
	Grand total	17,391,304	2,608,696	20,000.000

SPECIAL RESOURCE CENTERS

Mr. Fogarty. Your special resource centers are budgeted for $5 million in 1962, and you are asking for the same in 1963. What are these special resource centers?

Dr. Hunt. About 60 percent of these funds or maybe as much as two-thirds will be used to support computer centers. These centers are for the application of biomathematical methods, particularly electronic computers to biomedical research problems.

RESEARCH VALUE OF COMPUTERS

Mr. Fogarty. Give me an example of how a computer helps in research.

Dr. Hunt. Well, many kinds of biological data come from the laboratory in a form which suggests that a number of factors have gone into the production of a given result. If these are analyzed by ordinary arithmetical methods by hand, or even with the use of calculators, it might take weeks or months to analyze the data, or it might be impossible.

With a computer, the arithmetical processes are done so fast, that you can set it up to get a correlation very quickly of the various factors that might have produced the data and produced the results, with the results that were obtained.

PERINATAL STUDY

Dr. Shannon. Can I give a more concrete example?

Mr. Fogarty. Yes, use words that I recognize and can reuse myself sometime.

Dr. Shannon. Yes, sir.

In the perinatal study, the aim and objective is to observe, both before and after birth, some 50,000 pregnancies and births. This will involve records of a mother and of each child throughout the pregnancy and for about 6 or 7 years after birth. Each case will involve medical histories, systematic examinations, and laboratory studies. For example, the events that take place immediately prior to and during labor are carefully observed and recorded—anything that happens during the labor, the degree of anoxia and things of that sort.

This constitutes a large mass of data for each birth. These data must be analyzed to see what factors are generally related to bad outcome of the pregnancy. Take a very simple example: labors that occupy a period of 24 hours or more are suspect because the fetus is more susceptible to trauma during a long labor.

So one would take the cards and tapes representing the 50,000 cases and correlate the length of labor with adverse results—brain damage, say. If one finds more brain damage in the long-labor group than in the short-labor group, one would study such other factors as the age of the mother, the duration of pregnancy, whether it was early, whether it was late, the weight of the baby, whether there was observed jaundice after labor, whether the mother had a stormy course or the child had a stormy course during the first 7 to 10 days. All of this comparison and correlation is made possible by machine analysis.

The number of observations is so large that the job cannot be done by hand and only a portion of it could be handled by IBM card sorting machines. The amount of data is so large that it would take card-sorting techniques of the old IBM machines literally months to run analyses of this sort.

When you have large masses of data—this project involves several million cards—one must have some sort of very rapid automatic processing. The computer must be used for such a purpose.

Mr. Fogarty. So it is not only timesaving in something like this, but it is a saving of personnel?

Dr. Shannon. It would be impossible otherwise, sir.

Dr. Hunt. Actually, it does things you cannot do any other way.

Mr. Fogarty. I see.

Dr. Shannon. They are basic.

MULTIDISCIPLINARY CENTERS FOR RESEARCH ON AGING

Mr. Fogarty. Tell us about the multidisciplinary centers for aging research?

Dr. Hunt. There are five of those now.

Mr. Fogarty. Is there any connection between the grant that was given Brown and your being a Brown graduate?

Dr. Hunt. I am happy to say, sir, that I had nothing to do with the review and approval of that program. I was also happy to have my alma mater come through.

Mr. Fogarty. I see. That is a good answer, and it is a good school.

Dr. Hunt. The five multidisciplinary centers started with the one at Duke, activated something over 4 years ago, and there are——

DUKE MULTIDISCIPLINARY CENTER

Mr. FOGARTY. Explain just what you mean by this multidisciplinary center for aging research.

Dr. HUNT. The Duke center is not only the earliest but possibly the best example, because it involves the whole university.

Mr. FOGARTY. You mean it is better than Brown?

Dr. HUNT. It is broader and it involves the whole university, and Duke has a medical school, which Brown does not yet have.

Mr. FOGARTY. They are going to have one?

Dr. HUNT. It is in the process.

But until they have one, Duke has certain departments which are not——

Mr. FOGARTY. So when they get the medical school, they could be better than Duke. They ought to have a medical school by next September?

Dr. HUNT. Yes, sir.

Mr. FOGARTY. Go ahead.

Dr. HUNT. The Duke center is now in its fourth year. They have had more than 30 separate new research projects. These include a study of what they call an interdisciplinary health team, where they had physicians, nurses, psychologists, and other supporting paramedical personnel, working with older persons coming to the outpatient clinic at the hospital. They have done studies on preretirement counseling, and then more biologically oriented studies of the aging nervous system, arterial disease in relation to age changes, studies of amino acid and fatty acid metabolism in relation to age, and intervertebral connective tissue alterations with age.

In many cases these studies have involved more than one department of the medical school of a university. Hence, the designation "interdisciplinary."

BENEFITS FROM MULTIDISCIPLINARY CENTERS

Mr. FOGARTY. What benefits have been derived in the 4 years; or is it too early?

Dr. HUNT. In 1961 they have actual publications amounting to over 35 different papers, and 19 additional papers have been accepted for publication and are in press.

It is, of course, a matter of interpretation as to how much help older people have gotten from any of these papers. But certainly it can be said that this group has been productive in respect to developing new knowledge about aging and aging people and the way they might or should be handled.

Dr. SHANNON. Mr. Chairman, could I add a point here?

I should like to look at it more broadly than Dr. Hunt did when he described the specific Duke program. When we say "multidisciplinary centers for aging," we mean aging both of the individual and the group, from the standpoint of the biology and the tissue changes which result in less physical capacity and from the standpoint of the behavioral aspects of aging; that is, the change in the attitude of the individual as he goes through the process and also the social and economic aspects. All these things interplay one with the other.

It is not enough to look at tissue changes without also trying to understand the attitudes of and the social forces that are brought to bear on the individual.

It is quite impossible to point to studies of this sort and say, "Because these studies have been successful, the following has been accomplished."

What is happening is much more subtle. The Duke operations, for example, is the focal point of the entire State study on problems of aging. They have a State commission. The studies that are undertaken at Duke are affecting the judgments of the entire State on planning they will undertake for the aged. The problems that come up in their planning commissions are thrown to the Duke group for consideration and advice.

So what, I think, is happening here is that in a sufficient number of focal points throughout the country, aging is being looked at from the standpoint of its biology, from the standpoint of personal attitudes and socioeconomic aspects, that we are getting a clearer understanding not only of the problems of the aged, but also of what can be done to modify them. I think we are evolving a more intelligent attitude to the broad problem of aging throughout the country. Now, this is just beginning.

I think the net result of all of these studies will be a change in attitude and the progressive modification of the way in which we handle the aging without, however, our being able to say in a very specific way because we did this, this has happened.

I think if we do not realize this, we may be disappointed when we try to assess the value of an expenditure of that sort.

Mr. FOGARTY. Would you put those five centers in the record and where they are located?

Dr. HUNT. Yes.

Mr. FOGARTY. And the amounts of their grants?

Dr. HUNT. We will do that; yes, sir.

(The requested information follows:)

5 multidisciplinary aging centers supported by the National Institutes of Health, as reported by the Center for Aging Research

(1) Institution: Albert Einstein College of Medicine, New York, N.Y.:	
Fiscal year 1961 obligations	$288,909
Fiscal year 1962 estimate	260,159
(2) Institution: Brown University, Providence, R.I.:	
Fiscal year 1961 obligations	86,250
Fiscal year 1962 estimate	86,250
(3) Institution: Duke University, Durham, N.C.:	
Fiscal year 1961 obligations	345,754
Fiscal year 1962 estimate	359,076
(4) Institution: University of Miami, Coral Gables, Fla.:	
Fiscal year 1961 obligations	233,371
Fiscal year 1962 estimate	188,498
(5) Institution: Western Reserve University, Cleveland, Ohio:	
Fiscal year 1961 obligations	265,000
Fiscal year 1962 estimate	317,000

Mr. FOGARTY. What other activities are you engaged in in the field of aging?

Dr. HUNT. There have been a great many individual research projects which have been developed and come under NIH support in the last few years. The total amount of grants active on January 31, 1961, which we consider to be directly related to aging amount to nearly $6 million, and those——

SPECIAL STATEMENT ON AGING

Mr. FOGARTY. We shall put your prepared statement on these activities in the record.

(The requested information follows:)

SPECIAL REPORT: SUMMARY OF NATIONAL INSTITUTES OF HEALTH RESEARCH IN AGING, 1961

INTRODUCTION

The White House Conference on Aging, held early in 1961, focused additional national attention on the increasing number of older people in our population. Since 1900 the number of persons reaching the age of 65 has risen from 3 million to about 17 million. This is a jump of from 4 to over 9 percent of the total population.

As the number of people in the older age group has increased, so have the medical, social, economic, physiological, and psychological problems associated with aging. Parallel with this has been an increase in the amount of scientific investigation into such questions as how the various components of the body age, what changes occur in the functional systems of the human organism with advancing years, whether or not there is deterioration in the intellectual capacity of the older individual. There has been an increased emphasis on studies of the diseases which appear more frequently in older persons—cancer, heart disease, arthritis.

The National Institutes of Health, both through its intramural and extramural research programs, is contributing to this store of knowledge about the process of aging. The purpose of this document is to report on those programs of research in aging which are being supported in three broad areas: the behavioral and social sciences, the clinical sciences, and the biological sciences.

INTRAMURAL ACTIVITIES

The process of aging starts before birth and ends with death. Thus, any study of the phenomenon of life, of human growth and development, and of the diseases that affect mankind has a bearing on the study of aging. Two intramural programs of research at the National Institutes of Health are devoted specifically to the study of aging: the Gerontology Branch of the National Heart Institute and the Section on Aging of the National Institute of Mental Health.

In addition, investigations carried out by all of the Institutes affect in varying degrees the health and well-being of the aging person. These include research on the chronic disorders, such as heart disease, cancer, arthritis, blindness, mental illness, metabolic and dental disorders, as well as the infectious diseases.

GERONTOLOGY BRANCH, NATIONAL HEART INSTITUTE

The Gerontology Branch was established in 1941 to initiate one of the first programs in gerontologic research in this country. Housed in the Baltimore City Hospitals, it grew and developed as a part of the scientific and total community there, enjoying close cooperation and opportunities for valuable collaboration with the hospitals, the Johns Hopkins Medical School, and the University of Maryland Medical School.

An appropriation of $1 million was made in fiscal year 1962 for planning a new research building on land adjacent to the Baltimore City Hospitals. The new building will provide an unusual opportunity for the concentration of research on the problems of aging and will relieve congested laboratory conditions at the hospitals.

The present staff includes investigators trained in zoology, biochemistry, embryology, physiology, biophysics, medicine, nutrition, and psychology—and a supporting staff of trained technicians. This competent staff investigates all aspects of gerontology from the basic biologic processes of aging to the effects of aging on the total performance capacity of the individual.

Studies on cellular enzymes reveal that some enzymes concerned with energy production show decrement with age. Further work is in progress to determine methods for maintaining the activity of these enzymes.

In simpler animal forms and in tissue culture, the aging characteristics of the individual cells may be observed. In investigations of the biologic mechanisms of aging, studies of the fruitfly indicate that the rate of aging can be augmented by increasing the environmental temperature.

Long-range studies began in 1957 to record the aging process in normal persons living active lives in their communities. About 400 men, aged 24 to 99 years, spend 2 days every 18 months undergoing a series of psychological, physiological, and biochemical tests. Although the study is just beginning, certain facts about aging have already come to light.

For example, there is no evidence for sudden breakdowns in performance capacity at a certain age. Age changes accumulate slowly over the entire lifespan. Disability is not necessarily associated with aging. Many persons retain their vigor even into advanced ages.

Older persons, if they have the necessary dietary elements, can form new tissue and replace calcium in their bones. Learning ability is not lost in old age. With proper motivation, older persons can learn new tasks, but it may take them longer, and complex tasks need to be broken down into simpler units. Older persons are more susceptible to distracting factors than are younger ones. They are also slower in making adjustments.

Although increasing age is associated with a reduction in muscular strength, this is due in part to atrophy from disuse. Muscles that are used daily show little decrement with age. The amount of blood pumped by the heart diminishes with age, but it is adequate for normal activities. Different organs of the body wear out or break down at different times in the lifespan; and there are wide variations among individuals as to when this occurs.

A complete list of papers published or delivered by members of the staff appears at the end of this report in appendix A.

National Institute of Mental Health

Research on aging is carried out in the Institute's Section on Aging and through its collaboration with the Laboratory of Clinical Science and the Laboratory of Social Environmental Studies.

Current experimental studies carried out in the Section on aging involve both humans and lower animals. The facilities of the section are organized for research on behavioral capacities in relation to age and to concomitant physiological changes. The section continues to have two primary foci: (1) the gathering and organization of information on behavioral and physiological changes of aging, (2) investigation of impairments in higher cognitive functions in man, and their modification.

A completed analysis of data obtained during the past 2 years suggests that the age change in slowing of response tends to have the attribute of a general psychological process. That is, whereas young adults tend to show task-specific adjustment of response speed, older persons tend to have a speed of psychomotor performance more characteristic of them as individuals. The principal data on which these conclusions are based were obtained from the use of an apparatus designed and constructed at the NIMH, called the psychomet. Publication of the findings will be in the next issue of the journal Gerontologia under the title: "Age Differences in Response Speed as a Function of Controlled Variations of Stimulus Conditions: Evidence of a General Speed Factor."

Because of the implications of the findings and their relevance to psychophysiological changes in the normal adult, the Federal Aviation Agency requested and was granted the use of the apparatus in their current research on aging in civil airplane pilots. That Agency has completed the examination of 160 subjects using the apparatus and the results are now being analyzed in cooperation with the Section on Aging and the Biometrics Branch. Preliminary results also indicate significant age trends in the psychological measurements. Surprising is the fact that the trends are appearing in relatively young healthy men. The further analysis of the data as well as new studies will explore possible physiological bases for the changes. The suspicion that the observable behavioral changes may precede later-to-appear physiological changes is of considerable importance. Thus, there is the research problem of determining the extent to which the behavioral changes of advancing age are premonitory and predictive of length of life and disease states.

A comparison of two contrasting age groups of adults with respect to their performances on the standard problems programed by the logical analysis device (LAD) revealed a striking impairment of heuristic, i.e., inquisitive, behavior in the aged. Additional tests with special, simplified LAD problems failed to bring this form of task within the capacities of the older subjects. During the current year a heuristic evaluation and logical problem programing device was constructed in the section and preliminary observations were made at several levels of difficulty on young and old normal adults, on schizophrenics, and on children.

It is not clear what, if any, is the role of speed in the previously reported substantial age differences in logical problem solving. It is expected that present work will make further contributions toward the delineation of the mechanisms of aging in the central nervous system and behavior, particularly with regard to higher cognitive processes.

Nearing the completion is a followup study of a group of men over the age of 63 who have been intensively studied from psychiatric, psychological, social, medical, and physiological points of view. The report of the initial work is now in final draft by the collaborating investigators from the Laboratory of Clinical Sciences, Laboratory of Social and Environmental Studies, and the Section on Aging. Findings show a relation of health to psychological functioning. However, certain changes such as those noted in the individuals' social relations and in particular mental capacities do not stand in a simple 1-to-1 relation with measured physiological changes. Analysis of the recently obtained longitudinal data will throw light on some of the supposed cause-and-effect relations in the mental and physical well-being of older persons.

A complete list of papers published or delivered by members of the staff appears at the end of this report in appendix B.

EXTRAMURAL ACTIVITIES

Division of General Medical Sciences

The Division of General Medical Sciences supports a variety of projects for aging research including three large multidisciplinary centers for aging research located at Brown University, Providence, R.I.; University of Miami School of Medicine, Miami, Fla.; and Western Reserve University, Cleveland, Ohio. Through these and other projects, the Division is carrying out a program primarily aimed at developing more information on the basic biological nature of the aging process in the cells and tissues of the body, in organs, and as related to enzymes and hormones. The work also includes investigations into the importance of genetics in the character of the aging process and in longevity. Studies on the influences of nutrition and on the effects of man's living and working environment also are being supported, along with investigations into better rehabilitation techniques for older persons.

Among the projects related primarily to aging being supported by the Division are studies for establishing criteria for nursing care required by patients with selected health problems and the major disease conditions usually cared for in the nursing home, anesthetic and postoperative care for the geriatric patient, the utilization of health and allied services by older persons, methods of rehabilitating the aged, and longevity of the offspring of the long lived. In addition to these, there are medical and biological studies on the biochemical criteria for senescence in tissue, the aging process at sea level and high altitudes, vascular changes in joints due to low oxygen tension, the effect of age and ionizing radiation on collagen, genetic aspects of radiation induced aging, responses of bone to change in age and function, biology of the aging skin, studies on connective tissues, effect of changes in enzyme levels of lifespan, hormones in development and aging of tissues, and many others.

The NIH Center for Aging Research is a branch of the Division of General Medical Sciences. The report of this unit follows.

Center for aging research.—The Center for Aging Research, established in 1956 and now a part of the Division of General Medical Sciences, serves as the focal point in the National Institutes of Health for research in aging. Specifically, the center stimulates and assists the development of new research projects in gerontology at universities, medical centers, and various other research institutions in this country and abroad: maintains liaison with the NIH intramural and extramural programs, with other bureaus and divisions of the Department of Health, Education, and Welfare, and with other Federal agencies and organizations supporting programs in aging; fosters the training of additional research personnel; collects and disseminates data related to research in aging; and sponsors conferences, symposia, and seminars on research and training problems in the field of aging. Through its review of grant applications to the NIH and annual tabulation of active research projects, the center functions to point up areas in the field of gerontology needing new or additional emphasis.

Six percent of the total NIH grants to scientists in other countries were for research in aging. Currently, there are 25 active projects in 14 countries: Belgium, Canada, Chile, England, France, Italy. Israel, Japan, Puerto Rico, South Africa, Sweden, Switzerland, the Netherlands, and Yugoslavia.

The rapid increase in the number of NIH-supported projects reflects the developing interest of competent researchers in this field. A current analysis of these projects shows that more research emphasis on the psychological and social aspects of aging is needed. Presently, the majority of all research projects in aging relate to the physiological and biological aspects of aging.

The center seeks to coordinate the many activities in the field of aging research conducted or supported by the various Institutes and the Division of General Medical Sciences, National Institutes of Health. It also maintains liaison with other divisions of the Public Health Service and constituents of the Department of Health, Education, and Welfare which have an interest in this area. During the year the center worked with members of the Federal Council on Aging—including the Department of Health, Education, and Welfare—the Department of Agriculture, U.S. Civil Service Commission, Department of Commerce, Housing and Home Finance Agency, Department of Labor, Small Business Administration, Department of the Treasury, Railroad Retirement Board, and the Veterans' Administration.

One of the most important cooperative projects assisted by the center was the White House Conference on Aging. Ten other national meetings were participated in by center personnel.

Through fostering the development of university and medical school centers of research in aging, the center hopes to bring additional investigators into the field of gerontology. Such multidisciplinary units offer better opportunities for organized training programs or on-the-job training.

A function of the center which is receiving major emphasis is the collection and dissemination of information to the professions and the general public. In addition to its three annual publications, "Activities of the National Institutes of Health in the Field of Gerontology," "Research Highlights in Aging," and "Research Programs in Aging," the center distributed several mimeographed prepublication editions of Russian translations; a new brochure for general practitioners and others, "The Aging Patient"; White House Conference publications; and numerous miscellaneous materials on aging and the aged.

The response to the brochure, "The Aging Patient," was so notable that a series of these documents is now planned. A second volume on the cardiovascular diseases of the elderly is now being prepared for publication. This series features staff members of the large multidisciplinary centers for aging research giving the latest research information available to a general practitioner through the means of a roundtable discussion.

An exhibit on the functions of the center was shown at four national meetings: American Public Health Association, American Hospital Association, American Medical Writers' Association, and Federation of American Societies for Experimental Biology, and at the NIH Clinical Center.

The information program of the center also includes preparation of press releases and announcements, the dissemination of background information to press, radio, and television producers, and the dissemination of background information to editors and free lance writers. Several companies making films on aging received background information and materials from the center.

At the conclusion of this report are five tables covering the growth of the grant program in aging, reflecting the activity of each Institute and the Division of General Medical Sciences since 1958.

Interdisciplinary research centers.—Included among the many grants for extramural research in aging are the five major multidisciplinary centers for aging research located at Duke University, Durham, N.C.; Albert Einstein College of Medicine, New York City; Western Reserve University, Cleveland, Ohio; University of Miami School of Medicine, Miami, Fla.; and Brown University, Providence, R.I. The Center for Aging Research assisted in the programing for each of these centers.

Duke University: Duke's center, now in its fourth year, has launched more than 30 new research projects. These range from a study of the "interdisciplinary health team," preretirement counseling, the aging nervous system, and coronary artery disease in relation to age changes, to studies of aminoacid and fatty acid metabolism in relation to age, and intervertebral connective tissue alterations with age. Detailed progress reports and more than 30 scientific publications have resulted from the program.

Monthly seminars on aging are presented by prominent visitors, and are published annually.

About 20 scientists at the predoctoral and postdoctoral level are participating in the program and are receiving training.

In addition to the support by grants from the National Institute of Mental Health and the National Heart Institute, the program is also receiving support from the Ford Foundation. The Ford grant provides support for sociologists to extend their work into those aspects of aging not so directly related to health.

Albert Einstein College of Medicine: The Unit for Research in Aging at the Albert Einstein College of Medicine is conducting studies concerned with connective tissue changes with age, membrane physiology, genetic factors in aging, blood coagulation, arterial wall metabolism, aging of the red blood cells, and a variety of other studies, including problems of aphasia, emphysema, and rehabilitation. The manifestations of aging at the transition period between adolescence and adulthood are being studied.

Two seminar programs are conducted, one for investigators and one for the entire school.

Sixteen studies are underway, and nine individuals are receiving predoctoral or postdoctoral training in the program.

The facilities in the Van Etten Hospital, including both the wards and research laboratories, represent cooperative support from both the NIH through the National Institute of Mental Health, the National Heart Institute, and the National Institute of Arthritis and Metabolic Diseases, and the city of New York.

Western Reserve University: This program is seeking to coordinate research in biochemical, biophysical, and clinical aspects of aging; to stimulate interest in aging on the part of medical students, house staff, and developing investigators; to serve the Great Lakes region as a resource for information relating to aging; and to develop a measure of functional age in the individual.

Two chronic disease hospitals are furnishing subjects for investigation. At present, the first year's funds are committed to about a dozen projects, several of which are unique—for example, studies of aging in human placental tissue—and involve collaboration by several disciplines.

This center is supported by a grant from the Division of General Medical Sciences.

University of Miami School of Medicine: The novel characteristic of this program relates to its coordinated approach to the study of aging in the nucleus, cytoplasm, cell membrane, and intercellular substance.

In addition, comparative studies of model systems of aging in the various species are being launched. For example, in the undergraduate university, botanists are tackling the mechanism of aging in plantlife, while in the medical school, scientists in the preclinical disciplines are studying aging in various species of vertebrates, and in the Marine Biology Laboratory, certain invertebrates and lower vertebrates are receiving attention.

Plans call for the expansion of the program at the clinical level.

This center is supported by a grant from the Division of General Medical Sciences.

Brown University: This is the newest of the five centers and receives its support through a grant from the Division of General Medical Sciences.

The initial emphasis in this program is on the socioeconomic factors associated with aging, and the assessment of the relationship between these factors and the medical and biological aspects of aging and old age.

Investigators have the unique opportunity to utilize a well-defined population group within the compact borders of the State of Rhode Island for this study. The departments of economics, sociology and anthropology, biology, and psychology, all currently engaged in aging research, are contributing to the project. The hospital facilities in the community are being used for clinical research purposes.

National Heart Institute

Changes in the heart muscle and in blood vessels caused by aging have far-reaching effects on total human performance. Realizing this, the National Heart Institute became a pioneer in the support of gerontologic research and developed one of the most comprehensive programs of scientific investigation into aging. This vital research activity provides a background of gerontologic knowledge and productive research studies that make it a national and international resource in the field.

The projects supported by NHI range from basic research on aging in such short-lived lower organisms as the paramecium to integrated cooperative studies of elderly persons. Scientists are investigating the influence on the aging process of diet, heredity, changes in hormone production, and changes in connective tissue, as well as the mechanisms of cardiac failure in persons over 65 years and the rehabilitation of elderly cardiovascular patients.

The National Heart Institute, working with the Atomic Energy Commission and the American Institute of Biological Sciences, continues to support research conferences on the relationship between radiation and aging. Highlights of some of these meetings were published in July 1961 by the Federation of Societies for Experimental Biology. They appeared as a supplement to the Federation Proceedings entitled "Radiation and Aging: Synopses of Panel Discussions Held During 1958 and 1959."

The Fifth International Congress of Gerontology, and the publication which will result from the meeting, was supported in part by the National Heart Institute.

National Cancer Institute

Cancer occurs so commonly among elderly persons that it is inseparable from other problems related to aging. With the exception of a few malignant diseases that develop only in children, the incidence of every form of cancer increases with age. Long considered primarily a disease of children, leukemia actually strikes many more adults, and at an increasing rate; but in children it is usually more acute, and the survival period is shortened.

One of the most perplexing problems is that of the relationship of cancer development to changes that occur in the hormonal functions in the middle and later years. An investigation supported by a grant from the National Cancer Institute for a number of years has been concerned with the problem of cancer of the prostate gland, one of the most common tumors of older men. These studies have been accumulating biological data on aging males and have revealed that prostatic cancer becomes manifest clinically in man at a period in life when sex hormone production has become spontaneously greatly diminished.

Interpretations of findings in studies of hormone factors influencing the origin and growth of neoplasms are constantly being revised. Growth, whether normal or malignant, is the product of the chemical machinery within the cells. As this machinery is better understood, the process of aging will be more clearly defined and cancer will be brought under more effective control.

National Institute of Allergy and Infectious Diseases

The National Institute of Allergy and Infectious Diseases, through its research grants program, supports a variety of projects designed to give insight into the physiological and biochemical aspects of the aging process.

One study has been undertaken to determine the bacteriological and immunological factors occurring in urinary tract infection, with specific reference to pyelonephritis. This investigation reflects a major interest of the Institute of Gerontology at the University of Miami with regard to host factors that predispose to infection in the aged. Pyelonephritis is an important cause of debilitation and death in elderly persons, and this study is directed to understanding this disease.

An entomological study at Fordham University is concerned with the biological effects of parental age in insects. Since general biological principles are involved, this project may produce clues to the causative factors in aging and the degenerative diseases associated with it.

Grantees at the University of Rochester are studying the effect of aging on susceptibility to virus infection in an attempt to understand the general mechanisms responsible for susceptibility or resistance both at the cellular and animal level.

In studies at Boston University, grantees are concerned with viral infectivity effects on the central nervous system. It is hoped to determine the factors, varying with age, which influence resistance of specific tissues to certain neurotropic viruses.

A number of other fundamental studies on allergic or infectious processes may provide valuable secondary information on growth, maturation, and degeneration in both single cells and whole organ systems.

National Institute of Arthritis and Metabolic Diseases

Institute-supported studies are concerned with various aspects of diseases associated with aging, notably, osteoarthritis and osteoporosis. Other extramural studies which pertain to aging include changes in articular cartilage, the effect of aging on collagen formation and on mineral metabolism, the effect of age on skin metabolism and nutritional factors in chronic illness and in aging.

The Institute also participates in the support of a comprehensive program of research in aging at the Albert Einstein College of Medicine, New York City.

Within the Institute there are a number of research activities in which certain aspects of the aging problem come into consideration. The long-term complications of diabetes as these are seen in the blood vessels and kidneys resemble the changes which occur in aging. These are being studied both at a clinical and laboratory level. The underlying defects in transport of fatty materials and the clinically related situation in obesity are also under laboratory scrutiny.

Postmenopausal and senile osteoporosis is a very common disorder. Studies conducted in the Institute using metabolic balance and isotope techniques have revealed normal rates of calcium deposition in this disease pointing to excessive demineralization as the major etiologic mechanism. The benefits of high calcium intake in this condition continue to be studied.

The aging experimental animal has served as a useful model in the study of degenerative joint disease. The role of nutritional and endocrinologic factors as well as the participation of obesity in the development of joint changes have all been studied in the experimental animal. Similarly, the aging rat has been studied with respect to the effect of exposure of simulated high altitude. Such exposure has been found to decrease life expectancy and to favor myocardial damage.

The aging of tissues and cells has also been a fruitful field of study. The lifespans of red and white cells in the blood of animals of various species has received considerable attention. The effects of such agents as ionizing radiation and intense erythroid stimulation upon the age of circulating cells have been mentioned. Since the lifespan of certain of these cells is very great, observations over a period of many years are required for their accurate evaluation. Thus, the lifespan of the erythrocyte of the turtle has been under observation for a period of 7 years.

The continued capacity of a tissue such as the liver to generate enzymes adaptively has been under study. Specifically, it has been shown that the levels of enzymes concerned with urea synthesis remain susceptible to adaptive influences during adult life. Histological changes during aging have also been observed. Thus, there appear in various epithelial cells cytoplasmic organelles which may be lysosomes. These particles, absent in the tissues of the young animal, appear in later life and are suspected to contain predominantly lytic enzymes.

NIAMD continues through its laboratory of experimental pathology to maintain an active interest in the diseases of the American Indian. Due largely to the decrease in tuberculosis, the average age at death of this population is due to increase markedly over the next several years. It is expected that this population will prove of unusual interest in the study of the relationship of population age to disease incidence.

National Institute of Dental Research

Scientists in the Nation's dental schools and at the National Institute of Dental Research are interested in the phenomenon of aging as related to oral health, since all living cells, tissues, and organs change progressively with the passage of time.

Studies of experimental infections with oral micro-organisms have focused on the isolation, purification, chemical analysis, immunological reactivity, and physiological effects of bacterial endotoxins, and related physiological processes that may contribute to periodontal diseases. Investigators now believe that in view of the present knowledge of subtle, long-term systemic effects of bacterial endotoxins, the considerable amounts estimated to be present in the oral cavity may well have a broader significance than their contribution to the inflammatory process and soft tissue lesions seen in periodontal disease.

The process of mineralization that continues throughout life is of particular interest to dental and medical scientists. However, the underlying factors that regulate normal and pathological calcification in certain tissues are still not clearly understood. Recent experiments by dental scientists have shown that normally noncalcifying tissues will undergo mineralization when implanted with bacteria in the peritoneal cavity of rats. This technique has opened the way for studying the mechanism of calcification under highly controlled conditions.

National Institute of Mental Health

Aging ranks among the most important areas of scientific inquiry supported through the research grant program of the National Institute of Mental Health. Since its inception in 1948, the Institute has awarded 210 research grants for a total of $5,614,316 in the field of aging; this amount represents 5 percent of the total awarded to date.[1] The projects currently supported by the Institute total $1,383,369; the importance placed on this area is reflected in the fact that the average grant for research in aging ($32,937) is very nearly $10,000 higher than the average grant in the overall program.

The skills of investigators in the biological, medical, psychological, and social sciences are represented in the variety of projects supported as part of the NIMH research program in aging. The total effort, including basic as well as clinical studies, is directed at a solution of the manifold problems faced by older persons in their physical, intellectual, emotional, and social functioning.

Among the biological oriented studies are a number in which investigators are focusing on the effects of the aging process on the central nervous system. In one study an attempt is being made to determine how neurological changes in the aged are related to personal and social adjustment. From an analysis of detailed medical histories, psychological test results, and observations in the community, the investigators are defining how physiological, psychological, and sociological phenomena are interwoven in the behavior and adjustment of older persons.

A number of studies supported through NIMH research grants involve an exploration of how aging affects the individual's intellectual functions. In one project, for example, a series of experiments is being conducted to determine the extent to which a weakening in certain abilities; for example, to perceive, develop abstract concepts, and solve problems is due to self-disparaging attitudes learned from society's evaluation of older people. The investigators' hypothesis is that decrements in perceptual and cognitive skills among the aged are due to psychological and social factors rather than to the biological effects of aging.

The needs of the emotionally or physically handicapped older person are the subject of concern in a variety of projects in which therapeutic techniques ranging from drugs to cooperative community activities are being evaluated. In one large-scale study, investigators are identifying some of the specific therapeutic effects of psychopharmacological agents on a sample of institutionalized older persons. In another project, a community nursing facility is being organized and assessed as a substitute for institutionalization in a State mental hospital; the overall objective here is to provide care and treatment for the aged in an appropriate physical facility, while utilizing community medical resources and maintaining the patient's ties to his home and family.

Several studies supported through NIMH grants are devoted to determining what changes in environment can be effective in arresting or reversing the negative psychological and somatic aspects of aging. A research team in one study is designing an optimal housing development for older people, constructed around a small community center with educational and counseling facilities; the aim here is to find a means for making senior citizens an integral part of the community's social structure. In another project, a workshop for older unemployed persons has been established with the objective of using a productive work situation as a treatment method to restore those feelings of personal worth which appear to be an important ingredient of successful aging.

Of special note are the studies in aging being conducted as part of the expanding NIMH international research grant program. One tripartite study will permit international comparisons of important social aspects of aging in the United States, England, and Denmark. By using comparable sampling techniques in each country, investigators will be able to contrast aged persons in terms of, for example, their general level of physical functioning; services necessary to maintain the aged in their homes; sources of income; reasons for retirement; the role of the family in later life; and differences in life situations between persons over and under 75. In another study, a series of seminars has been initiated on international research in human development including patterns of aging; one of the goals here is to identify important areas for collaborative; cross-cultural research.

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[1] As of Sept. 1, 1961.

The studies noted here represent examples of how the National Institute of Mental Health is pursuing its research mission in the public health problem of aging. In their basic, experimental work in the behavioral sciences, investigators supported by the Institute are providing data to better understand the biological and social dynamics of aging; and, through their clinical studies, they are establishing new techniques of treatment, care, and rehabilitation that will permit the aged to maintain meaningful and rewarding roles in the community.

National Institute of Neurological Diseases and Blindness

The NINDB research program relating to chronic neurological disorders of aging is divided into (1) the aging process in the central and peripheral nervous systems, and (2) studies of extrapyramidal disorders, such as Parkinsonism, and other involuntary movements generally associated with aging.

Efforts to explain the causes and mechanisms of the process of aging in the nervous system are being pursued primarily through anatomical, developmental, environmental, biochemical, physiological, metabolic, and nutritional studies.

In both areas, pathological states are being observed in an effort to define the pathogenesis and possible etiological factors. Clinically, efforts are directed toward the ultimate prevention and repair of the aging process of the nervous system, and toward the diagnosis, treatment, prevention, and rehabilitation of the chronic neurological disorders of aging. In addition, studies are being pursued in some areas to establish new or improved research instruments and techniques which may open previously closed or limited avenues of research in this difficult field.

Process of aging

Studies of the process of aging of the nervous system deal primarily with associated structural alterations through the quantitative study of changes in the amount of nervous tissue with age; intracellular changes in the neuron, or nerve cell; and the changes in the interneuronal substance.

Quantitative changes are significant since any lack of renewal of degenerated nerve cells ultimately is associated with loss of function. Thus, grantee studies are underway to determine changes in cellular populations within cerebral cortex and cranial nerve nuclei. Another grantee has recently begun working with the flying-spot techniques, a new technical aid for the quantitative study of tissue. Using this tool, he hopes to develop methods for automatic counting of nerve cells.

Changes within the neuron are important since they will help estimate the degree of loss. Aging changes have been described in any areas, but the only intraneuronal change with aging agreed upon is appearance of the so-called senility pigment. There is greater need for a clear definition of aging pigment and an explanation for its occurrence. The relationship of pigment deposition in nerve cells with age is being explored in specific areas of the cortex and frontal lobe of the brain. Attempts are being made not only to determine the exact nature of the pigments by chemical methods, but also experimental procedures are being sought to produce the pigments in other cells of the body besides the neuron.

Regarding the intercellular studies, it appears that any alteration occurring in the space containing the fluid from which the nerve cells gain nutrient would be of great importance. Nevertheless, morphological changes of this space with respect to age are practically unknown. By means of the interference microscope, changes in cellular volume in relation to aging are being explored.

A second important avenue of research is the associated biochemistry of the nervous system since structural changes may ultimately be explained on a molecular basis. Changes in brain composition that accompany development have been of great interest to the neurochemists, but relatively little work has been done on the biochemistry of the aging brain. Slow decreases in such things as total nitrogen, proteins, the various lipoidal or fatlike substances, potassium, and inorganic phosphorus have been noted with aging. On the other hand, the concentrations of water, sodium, and desoxyribonucleic acid (DNA) increase with age, as do those of calcium and sulfur. As NINDB investigators turn their attentions to such matters, it is hoped that the meaning of these and other changes will become clear.

Some scientists involved in investigations of the metabolism of brain protein have been studying the effect of age on the amino acid composition of brain protein. Meanwhile, still others are working on esterases with the hope of gaining some insight into the role these enzymes play in the maintenance and metabolism of nervous tissue. An investigation of human brain lipids from normal aged persons and from patients with nervous disease is being carried on by NINDB grantees. Others are making comprehensive studies of brain lipids which include studies on brains in different stages of development and aging. New methods for extraction, separation, purification, and identification are being developed, and the various lipid fractions are being examined. Under NINDB, scientists are studying the metabolism and pathology of brain glycolipids. Radioactive isotopes are being used to label the compounds studied and to help elucidate their metabolism and turnover rates.

NINDB grantees, investigating the neutral metabolism of the rat in senescence, have shown preliminary evidence of an age-related reduction in the amount of ribonuclease-hydrolyzable, or decomposing, material in both cardiac muscle and Purkinje cells, the large branching cells of cerebral cortex. They are now verifying these results by spectrophotometric measurement of extracted DNA.

Attempts are being made to identify various other etiological factors in the aging of the nervous system, including the role of x-irradiation in aging; the function of the oxidative enzyme systems and brain respiration; and the aging of nervous functions in relation to physical and mental stresses. In studies of effects of radiation it was reported this year that marked decreases were observed in cortical thickness and in brain weight of irradiated animals.

In an effort to understand physiological changes of the nervous system in relation to aging, some investigators are observing changes in electrical activity of cortical and subcortical brain areas in the course of maturation. Meanwhile, other investigators are concerned with explorations of integrative mechanism associate with muscle extension and cutaneous reflex activity. From such explorations they hope to learn more about features of tone, posture, voluntary and involuntary movement, etc. and their alterations in development and aging, as well as in disease.

NINDB grantees, therefore, in many diversified approaches are scrutinizing the anatomical and physiological bases of many involuntary movements and rigidity or muscle tone. In some instances the investigators are seeking physioanatomical correlates by attempting to produce the neurological states in animals by placing lesions in selected areas of the brain. Functional capacities of animals in which parts of the cortex have been removed are being observed.

Of significance are efforts to explore the interrelationships of fiber connections between a number of structures in the extrapyramidal system.

Meanwhile, other grantees are analyzing the abnormal physiological and anatomical states, themselves, by electrical recordings of the altered characteristics of spastic spinal motorneurons, and by histologic techniques in rigid experimental animals. An extensive review of the literature in relation to methods of tremor measurement, factors affecting tremor, and the physiology of tremor, was published by one grantee early this year.

Extrapyramidal disorders

The current intramural program of NINDB in aging is primarily focused on the extrapyramidal disorders and involuntary movements, especially Parkinsonism. Through the use of depth electrodes in regions of the basal ganglia (the massed nerve centers of the brain) proposed as sites for later therapeutic ablation, one team of investigators is hoping to learn more about physiological alterations underlying syndromes of involuntary movements. Other investigators have been engaged in clinical and pathological studies of Parkinsonism-dementia complex. In June of this year these investigators reported to the American Neurological Association that their early findings suggest Parkinsonism-dementia complex and amyotrophic lateral sclerosis may be variation of the same disease. The Parkinson-like side effects of ataraxic drug therapy, or tranquilizers, has been reported widely in the literature. However, it is not known whether the drug-induced Parkinsonian reaction is due to hereditary susceptibility, whether there is a biologic relationship between this acute, reversible symptomatology and the irreversible chronic process of Parkinson's disease, whether the difference of the two conditions is only a matter of degree, or whether the underlying pathology is the same.

In addition to these specific studies concerned with the process of aging of the nervous system and with extrapyramidal disorders, it is important to note that the National Institute of Neurological Diseases and Blindness reaches much further into problems of aging through its research in other neurological and sensory areas. Among these are programs relating to glaucoma, deafness, speech, and cerebral vascular disorders. These, of course, are related to but not restricted to aging.

EXTRAMURAL STATISTICAL SUMMARIES

The following tables show the number and annual dollar volume of research and training grants in aging that were active on January 31, 1962, January 31, 1961, January 31, 1960, January 31, 1959, and January 31, 1958. The fiscal year columns indicate the appropriation from which funds were derived to support these projects, although these tables essentially reflect calendar year activity. The date of January 31 was chosen in order to include the actions of the November meetings of the National Advisory Councils.

NIH research and training grants in aging, active as of Jan. 31, 1962

PRIMARILY RELATED TO AGING

Institute	Number	Fiscal year 1959	Fiscal year 1960	Fiscal year 1961	Fiscal year 1962	Total
General[1]	56	$83,288	$66,171	$854,602	$868,870	$1,872,931
NCI	13	---	8,988	120,231	267,674	396,893
NHI	71	---	41,288	996,980	1,524,322	2,562,590
NIAID	13	---	---	23,926	171,746	195,672
NIAMD	65	---	---	303,593	968,758	1,272,351
NIDR	19	---	---	96,730	143,799	240,529
NIMH	37	32,026	72,678	547,649	757,160	1,409,513
NINDB	32	---	---	117,683	389,336	507,019
Total	306	115,314	189,125	3,061,394	5,091,665	8,457,498

SECONDARILY RELATED TO AGING

Institute	Number	Fiscal year 1959	Fiscal year 1960	Fiscal year 1961	Fiscal year 1962	Total
General[1]	79	$15,592	---	$1,461,120	$1,775,670	$3,252,382
NCI	48	---	$13,800	431,450	699,223	1,144,473
NHI	172	---	12,898	6,120,472	4,363,948	10,497,318
NIAID	39	---	7,900	256,055	303,381	567,336
NIAMD	88	---	---	512,385	1,296,465	1,808,850
NIDR	30	---	---	243,413	317,742	561,155
NIMH	39	---	19,630	1,420,573	510,769	1,950,972
NINDB	78	---	8,050	396,158	1,719,370	2,123,578
Total	573	15,592	62,278	10,841,626	10,986,568	21,906,064

Active as of Jan. 31, 1961

PRIMARILY RELATED TO AGING

Institute	Number	Fiscal year 1959	Fiscal year 1960	Fiscal year 1961	Total
General[1]	36	$83,288	$411,525	$912,662	$1,407,475
NCI	14	---	77,951	155,318	233,269
NHI	70	12,282	277,087	1,363,169	1,652,538
NIAID	7	---	12,217	45,446	57,663
NIAMD	47	14,220	169,665	605,382	789,267
NIDR	12	---	44,861	145,250	190,111
NIMH	31	83,038	420,483	479,662	983,183
NINDB	28	---	111,699	315,451	427,150
Total	245	192,828	1,525,488	4,022,340	5,740,656

SECONDARILY RELATED TO AGING

Institute	Number	Fiscal year 1959	Fiscal year 1960	Fiscal year 1961	Total
General[1]	66	$17,879	$713,503	$1,363,558	$2,094,940
NCI	47	---	384,588	510,335	894,923
NHI	149	94,410	1,166,600	2,457,291	3,718,301
NIAID	32	9,878	68,459	294,085	372,422
NIAMD	70	---	192,140	1,173,791	1,365,931
NIDR	24	---	133,637	256,626	390,263
NIMH	24	---	309,278	388,808	698,086
NINDB	43	---	156,319	802,723	959,042
Total	455	122,167	3,124,524	7,247,217	10,493,908

See footnotes at end of table, p. 983.

Active as of Jan. 31, 1960

PRIMARILY RELATED TO AGING

Institute	Number	Fiscal year 1958	Fiscal year 1959	Fiscal year 1960	Total
General [1]	28	----------	$393, 851	$715, 276	$1, 109, 127
NCI	19	----------	82, 449	279, 697	362, 146
NHI	72	----------	316, 365	1, 400, 322	1, 716, 687
NIAID	4	----------	11, 215	18, 363	29, 578
NIAMD	42	----------	66, 659	567, 432	634, 091
NIDR	19	$14, 384	119, 919	88, 502	222, 805
NIMH	31	72, 678	485, 141	461, 129	1, 018, 948
NINDB	29	----------	131, 018	336, 498	467, 516
Total	244	87, 062	1, 606, 617	3, 867, 219	5, 560, 898

SECONDARILY RELATED TO AGING

General [1]	40	----------	$171, 519	$523, 515	$695, 034
NCI	38	----------	211, 577	469, 738	681, 315
NHI	117	----------	907, 711	1, 792, 053	2, 699, 764
NIAID	21	$18, 384	42, 811	192, 825	254, 020
NIAMD	49	11, 129	104, 670	888, 129	1, 003, 928
NIDR	24	8, 012	156, 697	316, 609	481, 318
NIMH	20	----------	190, 189	228, 416	418, 605
NINDB	29	----------	138, 977	509, 509	648, 486
Total	338	37, 525	1, 924, 151	4, 920, 794	6, 882, 470

Active as of Jan. 31, 1959

PRIMARILY RELATED TO AGING

Institute	Number	Fiscal year 1958	Fiscal year 1959	Total
General [1]	15	$18, 192	$532, 231	$550, 423
NCI	20	120, 021	424, 407	544, 428
NHI	60	227, 888	1, 034, 709	1, 262, 597
NIAID	3	20, 350	10, 010	30, 360
NIAMD	35	37, 148	453, 958	491, 106
NIDR	11	38, 785	60, 774	99, 559
NIMH	32	340, 344	514, 716	855, 060
NINDB	21	109, 706	190, 741	300, 447
Total	197	912, 434	3, 221, 546	4, 133, 980

SECONDARILY RELATED TO AGING

General [1]	14	$32, 000	$268, 910	$300, 910
NCI	31	180, 556	263, 353	443, 909
NHI	84	441, 079	1, 192, 186	1, 633, 265
NIAID	10	24, 833	81, 558	106, 391
NIAMD	32	50, 344	528, 042	578, 386
NIDR	19	148, 867	152, 760	301, 627
NIMH	6	43, 499	53, 397	96, 896
NINDB	11	17, 239	144, 508	161, 747
Total	207	938, 417	2, 684, 714	3, 623, 131

See footnotes at end of table, p. 983.

Active as of Jan. 31, 1958

PRIMARILY RELATED TO AGING

Institute	Number	Fiscal year 1955	Fiscal year 1957	Fiscal year 1958	Total
General [2]	9		$12,258	$249,419	$261,677
NCI	11		40,853	99,991	140,844
NHI	48		138,700	747,329	886,029
NIAID	None				
NIAMD	14		41,179	132,434	173,613
NIDR	7		29,821	30,122	59,943
NIMH	28	$23,686	162,972	440,641	627,299
NINDB	14		37,751	79,215	116,966
Total	131	23,686	463,534	1,779,151	2,266,371

SECONDARILY RELATED TO AGING

Institute	Number	Fiscal year 1955	Fiscal year 1957	Fiscal year 1958	Total
General [2]	5		$122,262	$81,951	$204,213
NCI	20		90,207	141,437	231,644
NHI	60		349,597	703,682	1,053,279
NIAID	7		2,501	60,574	63,075
NIAMD	21		82,181	192,470	274,651
NIDR	16		121,426	143,872	265,298
NIMH	6		38,298	35,706	74,004
NINDB	8		34,085	83,804	117,889
Total	143		840,557	1,443,496	2,284,053

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[1] Division of Medical Sciences.
[2] Division of Research Grants.

APPENDIX A—GERONTOLOGY BRANCH, NATIONAL HEART INSTITUTE

PUBLICATIONS AND PAPERS PRESENTED

1. Strehler, B. L.: Studies on the Comparative Physiology of Aging. II. On the Mechanism of Temperature Life-Shortening in Drosophila Melanogaster. J. Geront. 16: (1), 2–12, January 1961.
2. Shock, N.W.: Current Concepts of the Aging Process. J. Amer. Med. Assoc. 175: 654–656, February 1961.
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5. Buetow, D. E., and Levedahl, B. H.: Effect of Nitrogen on Testosterone Stimulation of Respiration in Euglena. (Abstract.) Fed. Proc. 20: (1), (Part I), 197, March 1961.
6. Fletcher, M. J., and Sanadi, D. R. The Dynamic Turnover of Rat Liver Mitochondria. (Abstract.) Fed. Proc. 20: (1), (Part I), 1946, March 1961.
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9. Olewine, D. A., and Barrows, Jr., C. H.: Random and Voluntary Activity Following Prolonged Dietary Restriction. (Abstract.) Fed. Proc. 20: (1), (Part I), 364, March 1961.
10. Barrows, Jr., C. H., and Roeder, L. M.: The Effect of Age on the Concentrations of Enzymes in the Livers and Kidneys of Normal Protein-Depleted and Protein-Repleted Rats. (Abstract.) Fed. Proc. 20: (1), (Part I), 371, March 1961.
11. Feeley, J. W., Lee, T. D., and Milner, W. R.: Pulmonary Vascular Resistance and Compliance Changes During Hypoxia in the Dog. (Abstract.) J. Clin. Res. 9: (2), 195, April 1961.
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18. Fletcher, M. J., and Sanadi, D. R.: Turnover of Liver Mitochondrial Components in Adult and Senescent Rats. J. Geront. 16: (3), 255–257, July 1961.
19. Searls, R. L., Peters, J. M., and Sanadi, D. R.: -Ketoglutaric Dehydrogenase. X. On the Mechanism of Dihydrolipoyl Dehydrogenase Reaction. J. Biol. Chem. 236: (8), 2317–2322, August 1961.
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1. Birren, J. E., and Morrison, D. F.: Analysis of the WAIS Subtests in Relation to Age and Education. J. Geront. 16: 363–369, 1961.
2. Birren, J. E.: A Brief History of the Psychology of Aging. Part I. The Gerontologist 1: No. 2, 69–77, 1961. Part II. The Gerontologist 1: No. 3, 127–134, 1961.
3. Birren, J. E., Riegel, K. F., and Morrison, D. F.: Age Differences in Response Speed as a Function of Controlled Variations of Stimulus Conditions: Evidence of a General Speed Factor. Gerontologia 5: No. 4, 1961.
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2. Birren, J. E.: Intellectual Capacities, Aging, and the Nature of Man's Environment. A Discussion of Issues and a Report of Experimental Findings. Aging Around the World. New York, Columbia University Press.
3. Bireen, J. E.: Age Differences in Learning of a Two-Choice Water Maze by Rats. J. Comp. Physiol, Psychol.
4. Botwinick, J., and Brinkley, J. F.: An Analysis of Set in Relation to Reaction Time. J. Exp. Psychol.
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7. Warren, R. M.: Some Pitfalls in Estimating Numerically the Lightness of Grey Papers. J. Exp. Psychol.
8. Warren, R. M.: Illusory Changes of Repeated Speech Sounds-Monaural vs. Binaural Listening. Aging Around the World. New York, Columbia University Press.
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APPENDIX C—INTERDISCIPLINARY CENTERS FOR AGING RESEARCH

DUKE UNIVERSITY

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1. Lazlo, John, Harlan, William R., Klein, Robert F., Kirshner, Norman, Estes, A. Harvey, Jr.: The Effect of 2-Deoxy-d-Glucose Infusions on Lipid and Carbohydrate Metabolism in Man. J. Clin. Invest. 40: 171–176, January 1961.
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3. Busse, E. W.: How To Handle the Elderly Hypochondriac. RISS 40, February 1961. Medical Economics, 38: 6, 104–108, March 1961.
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UNIVERSITY OF MIAMI

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ANESTHESIOLOGY

Mr. FOGARTY. Now, what about anesthesiology?

We did not discuss it last year, as I remember, but, when you went to the Senate, you were asked questions and I know the Senate had in their report that anesthesiology has been one of the most neglected of all the medical fields as far as research and training are concerned.

It is a problem that has been with us for a long time. But until the Senate mentioned it last year, our committee had not given this much attention. What are you doing this year? How much money was granted? Was this earmarked?

Dr. SHANNON. No, sir.

Mr. FOGARTY. All right.

Dr. HUNT. In 1960, there was one NIH-supported research training program in anesthesiology. In March 1961, 6 such programs, with 15 people in training, were reported to the Senate. At the end of December 1961, the Division of General Medical Sciences allotted $264,154 to support programs at 10 institutions where 25 people were in training for research in anesthesiology.

Mr. FOGARTY. Put the names of those 10 in the record, and if you have any further explanation, put it in the record, please.

(The requested information follows:)

SPECIAL REPORT: ANESTHESIOLOGY

BACKGROUND

Despite the great and growing importance of anesthesiology to medicine and to progress in medical and biological research, the best available estimate is that in 1961 there were no more than 150 individuals in the United States with adequate qualifications to teach and conduct research in this critically important field.

In recognition of this situation the Senate Committee on Appropriations[1] directed the Division of General Medical Sciences, National Institutes of Health, to "give special attention to the training of research anesthesiologists and to the support of scientific research projects and program grants in anesthesiology."

PRESENT STATUS IN RESEARCH

Problems in anesthesiology may be grouped in two classes, research and training. In the first category, for 1961, the National Institutes of Health supported 40 research grants in the amount of $696,622 and another 40 closely related grants investigating pain, drugs to relieve pain, and breathing and circulatory considerations in relation to anesthesia. These grants were divided among the NINDB, NIMH, NCI, NIDR, NHI, and DGMS.

Since most medical schools lack a department of anesthesiology, clinical reseach in this subject is commonly done in departments of surgery, pharmacology, and internal medicine. A few of the subjects under current study are: surgical anesthesia and postoperative care for old people, drug action in children as it affects preanesthetic medication and respiration during anesthesia, the effects of general anesthetics on healthy humans contrasted with surgical cases, and the pretesting of circulatory response to anesthetics in surgical patients to learn whether they can stand general anesthesia.

Laboratory research in anesthesiology is done in the same departments as the clinical research and, in addition, in departments of physiology, biochemistry and molecular biology. Examples of current interest in these various areas are: experimental studies of ether convulsions, effects of anesthetics on the inner ear (or hearing), mechanisms of action of local anesthesia on mammalian nervous tissue, gas exchange with uneven pulmonary blood flow, evaluation of muscular exercise as a resuscitative method, the influence of depressants on acetylcholine metabolism, and the formulation of a molecular theory of general anesthesia.

RESEARCH NEEDS

The many areas of anesthesiology requiring more research and knowledge include study of the physiology of consciousness and unconsciousness, and the use of hypnosis as a special adjunct to anesthesia, since many people fear anesthesia more than surgery. There is a need for long-term studies of the mechanisms of action and of the effects of drugs which produce muscle relaxation, amnesia, relief from pain, and unconsciousness, and of the secondary effects of these drugs on blood pressure, heart action, and breathing. The reactions of anesthetic and analgesic drugs among children and old people requires much further study because the physiological tolerance in these groups is less predictable and the problems are more diverse. There is a lack of specialized equipment, such as mobile units, suitable for disasters, and instruments to record and compare the activities of individual nervous and physiological reactions during anesthesia.

PROBLEMS IN TRAINING

To become a clinical anesthesiologist a trainee needs an M.D. degree, a year's internship, and a residency in anesthesiology of at least 2 years. This amount of preparation is not considered adequate to equip a person for clinical teaching beyond the basic level, nor for extensive research.

The Council on Graduate Medical Education of the AMA has reported that, in September of 1960, there were 241 approved residency programs among the

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[1] S. Rept. 618, June 25, 1961, p. 32.

6,876 hospitals in the United States. At this time these teaching hospitals were training 1,244 clinical anesthesiologists (79 percent of their capacity). Even so, it is estimated that perhaps as many as 40 percent of all the hospitals had physicians administering anesthesia, and less well-trained staff served in the balance.

Adequate preparation for conducting and teaching research in anesthesiology involves the training required for clinical anesthesiology plus additional study in the basic preclinical sciences of biophysics, biochemistry, and pharmacology, 1 to 3 years of personal research under a research anesthesiologist, and 1 or 2 years of teaching experience. This prolonged training is necessary because the scientific specialist must pay particular attention to surgical and obstetrical problems in the course of his medical education, and in addition he needs to know a considerable amount about instrumentation, and about the physics and chemistry of gases. He must have a broad grounding in pharmacology with especial reference to circulatory, respiratory, and liver changes in relation to drugs. He must be acutely observant in order to detect individual differences in reactions to drugs and their effects on unconscious people. In the nature of things such work moves across the classical boundaries of disciplines and departments, and is most likely to be carried out in academic environments where the long, expensive period invested in training is least likely to be financially rewarded.

PRESENT STATUS IN TRAINING

In 1960, there was one NIH-supported research training program in anesthesiology. By March 1961, 6 such programs training 15 people were reported to the Senate. As of the end of December 1961, the Division had allotted $264,134 to support programs at 10 institutions where 25 people were in training for research anesthesiology.

FUTURE DEVELOPMENTS

More emphasis must be placed on training men and women for research and teaching in anesthesiology. The approach against our present shortages must be broad and substantitive. Efforts to encourage and aid more young men to develop in this field must be expanded. There is no substitute for high quality training in research environments. Also, more effort must be spent investigating the fundamental problems of anesthesiology, especially as they relate to fields such as physiology, pharmacology, cardiology, hematology, obstetrics, surgery, and in fact, the whole field of medicine.

Training grants in anesthesiology, fiscal year 1961

No.	Program director	Institution	Amount paid
2G-56	Papper, E. M	Columbia University	$35, 919
2G-63	Cullen, Stuart C	University of California	36, 506
2G-215	Dripps, Robert D	University of Pennsylvania	38, 664
2G-165	Vandam, Leroy D	Harvard University	11, 858
2G-427	Gravenstein, J. S	University of Florida	10, 000
2G-668	Orth, O. S	University of Wisconsin	33, 333
2G-87	Baez, Silvio	Albert Einstein College of Medicine	24, 000
2G-770	King, Benton	University of Buffalo	25, 898
2G-699	Holaday, Duncan A	University of Chicago Clinics	30, 660
2G-862	Bunker, John P	Stanford University	17, 299
	Total		264, 137

NOTE.—The above training grants are listed in order of activation.

INSTRUMENTATION

Mr. FOGARTY. What are you doing in the area of instrumentation?

Dr. HUNT. This is another one of the programs where we are giving additional emphasis. There has been a certain amount of support in this area for many years. Much of it has been focused on the development of new instruments to aid in research. There is, in the field, a strong feeling that we should now get a great deal more sophisticated and apply new methods of solid state physics to biomedical problems. This is a new field, a developing field.

We called a small conference 2 months ago, primarily of biophysicists, to advise us on the whole question of biomedical engineering. At the moment it is not completely clear what direction this work should take or what the details should be. Every one agrees that there should be more research in it. No one is quite sure how the field should be defined or how it should be approached. We are working on it.

Mr. Fogarty. You are at least getting started.

Dr. Hunt. Yes, sir.

NURSING RESEARCH

Mr. Fogarty. What are you doing in the field of nursing research?

Dr. Hunt. The level of support of nursing research is now well over $1 million a year.

Mr. Fogarty. Why should this not be under Nursing Services and Resources?

Dr. Hunt. Under——

Mr. Fogarty. Miss Arnstein.

Dr. Hunt. It grew up as an NIH function because when the nurses first got authority to support research some 6 or 7 years ago, there was no mechanism in the Bureau of Medical Services, where nursing was then located, to handle it. So it was put under NIH administration.

And then the program went beyond any earmarked money that they had in Nursing, so it developed as part of the program of the Division of General Medical Sciences. It could very well be transferred one of these days.

Mr. Fogarty. All right. What are you doing now? How much are you spending?

Dr. Hunt. I can supply the exact figure for the record. It is well over a million dollars.

Mr. Fogarty. All right.

(The requested information follows:)

Nursing research grant support:	
Number of grants	45
Fiscal year 1961 obligations	$1, 399, 790

Dr. Hunt. The types of research vary considerably from studies of how nurses do their work on the wards to studies of what various kinds of nursing personnel can properly do, how much can be done by the aids, how much can be done by the trained practical nurses, how much has to be reserved for the trained nurses (the registered nurses), to more complex sociological studies of the place of nursing in the whole complex of medical care.

RESEARCH IN GENETICS

Mr. Fogarty. Tell us about your work in genetics?

Dr. Hunt. We have training programs in genetics, and we are supporting research. We hope to expand this support. We are not doing as much of it as we think should be done. But a start has been made.

Mr. FOGARTY. I was just trying to think who spoke about this the other day. Oh, yes; I think it was Dr. Shannon that mentioned the fact the other day that the New York Times devoted a whole page to this new discovery in genetics. So there is interest in this area.

Dr. HUNT. Oh, a great real of interest. And we are working on it actively.

Mr. FOGARTY. Will you supply, for the record, just what you are doing? And how much money you are spending?

Dr. HUNT. Yes, sir.

(The requested information follows:)

ACTIVITIES OF THE DIVISION OF GENERAL MEDICAL SCIENCES, NIH, IN THE FIELD OF GENETICS, AS OF FEBRUARY 15, 1962

The Division of General Medical Sciences, NIH, is supporting 33 research training grants in the field of genetics in the amount of $2,302,243, and 98 research grants in the amount of $2,316,217, for a total of $4,618,460.

The research training grants have been made to institutions across the country to assist in the development and improvement of their departments of genetics and to aid in the provision of training for graduate students in medical genetics, human genetics, mammalian genetics, cytogenetics, virus and bacterial genetics, biochemical genetics and others. These grants are providing support for at least 250 trainees.

The research grants in genetics are seeking directly to bring forth more information on the critical role the genes are known to play in the nearly all aspects of man's growth and development, his good health, or his tendency to disease, his intelligence, temperament, bodily vigor, and longevity. Scientific investigators are approaching the field from a number of standpoints. They are seeking more information about the precise manner by which the genetic mechanism transmits its information. This involves great amounts of work in the complex molecules of the chromosomes, deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). They are also studying genetics through statistical and population studies in which the descendants of one plant or animal cell are investigated for the variation that may be produced by viruses, radiations, chemicals, or other agents.

Population studies are being carried out at the level of the individual with colonies of insects and with people in investigations of the distribution of certain blood factors in various parts of the world. The hereditary resistance in plants and animals to chemicals and drugs is another aspect of genetics under consideration, and there is continuing interest in the causes and transmission of hereditary defects, not only those which produce obviously abnormal offspring, but those metabolic defects which influence body chemistry and cause blood defects and the loss of offspring before birth. There is work on the very difficult questions of how the cells of an individual recognize the cells from another individual of the same kind, and why the foreign cells are usually rejected. This is critical in studies of the transplantation of tissue and organs.

During 1961 more than 60 scientific papers were published by DGMS research grantees in the field of genetics, and a large number of papers were published also by individuals in the DGMS research training and fellowship programs.

NEW YORK TIMES ARTICLE OF FEBRUARY 2, 1962

Mr. FOGARTY. And if you can get a copy of the New York Times article you mentioned, we shall place it in the record, too.

(The article referred to follows:)

BIOLOGISTS HOPEFUL OF SOLVING SECRETS OF HEREDITY THIS YEAR

(By John A. Osmundsen)

Biology is undergoing a revolution whose meaning and magnitude have become apparent only in recent weeks. The pace has been so swift, in fact, that many scientists do not fully appreciate the potential of the powder keg they are sitting on.

This was the clear import of a statement made by a participant in a recent symposium on genetics, who compared the state of that field today with the state of physics in 1927.

"They were saying then that physics was dead, that all of the major problems had been solved," he declared.

He did not have to mention that the first atomic bomb was detonated just about 20 years later.

In drawing his ironic comparison between the two fields, the scientist was calling attention to cries being heard today that genetics is dead.

That assessment is based upon the great likelihood that the chemical code of inheritence, which determines the form and function of every living thing and thereby provides the basis for genetics, will be cracked before the year is out. Scientific reports at the recent genetics meeting, moreover, only added conviction to that prediction.

There is no doubt that the breaking of the genetic code will rank among the greatest scientific achievements of all time. What some scientists apparently do not realize, however, is that, instead of killing genetics, breaking the code breathes new life into that field and into all of biological science.

Indeed, it is safe to say that some of the biological "bombs" that are likely to explode before long as a result of that achievement will rival even the atomic variety in their meaning for man.

Some of them might be:

Determining the basis of thought, if, as many scientists are beginning to expect, memory consists of information stored in giant molecules according to the genetic code.

Developing remedies for afflictions that today are incurable, such as cancer and many of the tragic inherited disorders.

Controlling the inheritance, and hence the destiny, of plants and animals and perhaps even man himself.

Creating life, of a sort, from chemicals that today are in the bottles on the scientists' laboratory shelves.

It may be hard to imagine that a magic cipher of any kind could be so powerful. Yet, this is certainly part of the attraction that the problem of deciphering the genetic code has had for physicists—both theoretical and experimental—mathematicians, chemists, biologists of all kinds, doctors, and at least one astronomer and one political scientist.

CODE A VITAL LINK

The question they are all trying ultimately to answer is how living things get to be the way they are. The problem reduces to a matter of deciphering the code because that is the first step in the process that ends with the fully developed organism, whether tree, horse, or human.

This may be most easily appreciated if it is understood that the nature of the complete organism is determined by the interactions of all of its component cells, some acting one way, some another.

The character of each cell, in turn, is determined by the cell's chemical composition and the chemical reactions that go on inside it.

Those reactions and the formation of structural elements of the cell are controlled primarily by substances called proteins. These are large complex molecules made up of numerous subunits, called amino acids. And the function of each type of protein is determined specifically by the arrangement of the amino acids along the molecule.

Finally, the structure of every specific protein, that is, the order of the 20-or-so kinds of amino acid in the chain-like protein molecule, is established by other cell chemicals called nucleic acids.

STRUCTURE DETERMINES NATURE

This is where the code comes in. The directions for hooking together amino acids into specific proteins, which will determine the nature of every cell, and thus, of the whole organism, are encoded in the structure of the nucleic acids.

That code is embodied in the nucleic acids of the nuclei of egg and sperm when they unite to begin the history of a living thing.

The coded instructions for growth and development are then perpetuated throughout the lifetime of the organism when cells divide and specialize, giving bulk and identity to whatever they are part of.

This picture has been almost 100 years in the making. Almost all of the fine detail in it, however, has been supplied in the last decade and some of the most crucial strokes executed in recent weeks.

Thus has the pace in this fastest moving of all fields in science picked up as scientists near their goal of cracking the code.

A firm basis for the existence of such a code was not found until 1953, 87 years after the "functional unit of heredity," later called the gene, had been discovered by Gregor Mendel, an Austrian abbot.

That winter at Cambridge University in England, two young scientists named Frances H. C. Crick and James D. Watson, an American now at Harvard University, puzzled out the molecular structure of a substance, deoxyribonucleic acid, or DNA, that exists in the nuclei of all cells and, just a few years earlier, had been shown conclusively to be the carrier of the hereditary information.

The structure for DNA that they arrived at was a double helix, a form that resembles a twisted ladder. The side of the ladder, they found, consisted of alternate sugar and phosphate units. The rungs, between the sugars, were paired nitrogenous bases of four types: adenine, guanine, cytosine and thymine. Moreover, the bases paired in a very specific way, adenine with thymine only and cytosine only with guanine.

On the basis of that model, Dr. Crick and Dr. Watson were able to suggest mechanisms by which a DNA molecule performs its most notable functions: reproducing itself (replication) and carrying the genetic information.

The scientists speculated that the double-stranded DNA molecule might replicate by first unwinding and dividing into two long chains, in effect straightening out the ladder and splitting it lengthwise through the middles of the rungs.

COULD ACT AS TEMPLATE

Each half could then act as a mold, or template, on which a complementary strand could form. This might take place by the sticking of free nitrogenous bases in the cell to their corresponding ones on the halved-ladder mold, adenine sticking to thymine but bouncing off guanine and cytosine, for example.

In that way, a single DNA molecule would produce an exact copy of itself, resulting in two ladders with the same genetic information in both.

This was demonstrated in the laboratory in 1957 by Dr. Arthur L. Kornberg at Washington University in St. Louis. For this work the scientist shared the 1959 Nobel Prize in physiology and medicine.

But in what form was that information carried by the DNA? The Cambridge scvien-bases, paired so that each one formed half a rung along the DNA ladder, might provide the basis for a four-letter code—AGCT—to which instructions for protein manufacture could be consigned.

That is, one base (or group of bases) might encode one particular amino acid, the adjacent base (or group of bases) might encode another amino acid, and so forth along the DNA molecule.

The resultant chain of amino acids, complementing the sequence of bases, would then constitute the specific protein called for by the DNA.

CARRIER WAS SOUGHT

That was all very well, but it had been known for some time that the site of protein manufacture is the cytoplasm, or cell sap, and not in the nucleus, where the cell's hereditary instructions are kept in the form of DNA. This suggested that another substance was needed to carry the instructions from the nuclear DNA into the cell sap.

The most likely candidate for that job was another nucleic acid called RNA or ribonucleic acid. RNA was known to exist in the cytoplasm and to be associated with protein synthesis. And its structure was very similar to DNA's.

The most important differences were that most RNA was single-stranded and that it contained a nitrogenous base called uracil in place of DNA's thymine. Otherwise, they were virtually identical.

This suggested a possible mechanism by which the genetic information could get to the ribosomes—minute particles in the cell sap—where proteins are made. DNA could direct the synthesis of RNA in much the same way that DNA reproduces itself.

In that way, the coded instructions for protein synthesis that are contained in the structure of the DNA molecule could be transmitted to RNA through the ordered arrangement of bases in the DNA-synthesized RNA strand.

COULD TRANSMIT CODE

The RNA could then carry its instructions from the nucleus to the ribosomes in the cytoplasm. There, the long RNA copies of the DNA code could act as molds, or templates, on which amino acids could be laid down in chains of protein.

This theory—the role of a "template RNA" in protein synthesis—was put forth by Dr. Jacques Monod and Dr. Francois Jacob of the Pasteur Institute in Paris and has only recently been confirmed in experiments by Dr. Jerard J. Hurwitz and Dr. J. J. Furth of New York University and Dr. Paul Berg and Dr. William B. Wood of Stanford University.

That leaves three major questions: How do amino acids get to the ribosome, by what mechanism are they alined there along the template RNA, and what sequences of bases correspond to which amino acids in the code?

The answers to the first two have been determined, and the answer to the last will almost surely be known this year.

As to how amino acids get to the ribosome, Dr. Crick and other scientists speculated a few years ago that an "adapter" molecule of some sort might help. The discovery by several laboratories in 1957 of a type of RNA that was much smaller than template RNA, and recent experiments conducted on the basis of that finding, have identified the new RNA as the adapter.

CALLED TRANSFER RNA

Because of the adaptor's special function, it was dubbed "transfer RNA."

It works something like this: Special enzymes—protein regulators of biochemical reactions—were discovered by Dr. Mahlon B. Hoagland of Harvard Medical School in 1955 that activate amino acids. Transfer RNA molecules, 1 for each of the 20-or-so known amino acids, then pick up these protein building blocks in the sap and carry them to the ribosome.

But transfer RNA is not finished there. It also provides part of the mechanism by which the amino acids are properly alined on the template RNA.

It now appears that this is achieved by the mating of a particular group of bases on each transfer RNA strand with a complementary group of bases along the template RNA on the ribosome.

For example, the base sequence of uracil-adenine-guanine, or UAG, on the transfer RNA would mate with adenine-uracil-cytosine, or AUG, on the template RNA.

It was found that each amino acid attaches to one end of its particular transfer RNA. There are indications that the other end of that transfer RNA strand sticks to the template, like a foot. Thus, the amino acid is left dangling in a manner that allows it to join hands with similarly dangling ones on either side.

JOIN IN PROPER SEQUENCE

Once a full chain of amino acids has joined—in the sequence demanded by the template—the resultant protein peels off the ribosome ready to carry out its function in the cell sap, as an enzyme or hormone, for instance.

This seems to be exactly what happens, according to experiments conducted recently by Drs. Richard Schweet of the University of Kentucky and Howard M. Dintzis at the Massachusetts Institute of Technology. They found that some 150 amino acids of 1 type of protein lined up and linked together in about a minute and a half.

Thus, the sequential arrangement of amino acids in each specific protein reflects the genetic message encoded in the "master plan" of the DNA and passed on through the interaction of template and transfer RNA's.

This, however, does not say what the code is like—how many bases there are to an amino acid, what base sequences encode which amino acids, how this genetic information is "read out" of the base sequence, whether the code is universal or if different ones exist for different organisms.

It is on those problems that scientists lately have made the most spectacular headway.

CODE BELIEVED UNIVERSAL

First, they have produced convincing evidence that the code probably is universal, greatly simplifying the task of deciphering it.

Experimental evidence for this was cited during the recent genetics symposium at Indiana University by Dr. Fritz Lipmann of the Rockefeller Institute. He told of manufacturing normal proteins from a mixture of RNA from one kind of organism and of the cell sap, containing ribosomes, amino acids, and enzymes, from a completely unrelated organism.

The case for the universality of the code will be strengthened further if scientists can do that trick with normal cell sap and "unnatural," or synthetic, RNA's.

The ability to manufacture special RNA's of known composition was made possible by the discovery of an enzyme, called polynucleotide phosphorolase, that hooks RNA parts together. Dr. Severo Ochoa shared a Nobel Prize for that achievement in 1959.

It was through the use of that enzyme that one of the biggest advances in breaking the code was made. This was announced last August at a biochemistry meeting in Moscow by Dr. Marshall W. Nirenberg and Dr. J. Heinrich Matthaei, both of the National Institutes of Health in Bethesda, Md.

MANUFACTURED RNA

They used the enzyme to make a synthetic RNA, all of whose bases were uracil, then put that nucleic acid to work making protein in the test tube. What they got back was a protein that consisted entirely of one kind of amino acid, phenylalanine. They knew immediately that they had determined the nucleic acid coding for the first amino acid.

That is, a group of bases consisting exclusively of uracil—UU, UUU, UUUU, or whatever number of bases the coded comprised—was the designation for phenylalanine. Wherever such a group occurs in the RNA molecule, a phenylalanine will appear in the corresponding protein.

The synthetic RNA—called poly-U—has since been used by Drs. Peter Lengyel, Joseph F. Speyer, Carlos Basilio, and Ochoa at New York University and by the NIH team as a "handle" to determine the base composition of the RNA code for all 20 amino acids.

This achievement was revealed for the first time at the Indiana meeting.

The experiments were done by "doping" the poly-U with small amounts of the other bases—adenine, guanine, and cytosine—allowing the resultant synthetic RNA's to make protein and then analyzing the protein for its amino acid content.

VARIATIONS STUDIED

For example, the New York group added a very small amount of adenine to the poly-U and recovered a protein that consisted mostly of phenylalanine with traces of another amino acid, isoleucine.

The proportion of uracil to adenine in the poly-U RNA indicated that the code for isoleucine was two U's (for uracil) to an A (for adenine). It could not be determined however, whether the sequence was UUA, UAUU, or AUU.

Similarly, when more adenine was put into the poly-U RNA, small amounts of asparagine were picked up in the protein in addition to the expected phenylalanine and isoleucine. The proportions indicated this time that the code for asparagine was two A's to a U, though again the sequence could not be determined from the data.

The 2-to-1 composition of the base coding for the amino acids suggested that the code might be triplet in form, the four bases taken three at a time determining each amino acid.

Experimental evidence for this as well as other indications of how the code is read out were reported in the December 30 number of Nature by Dr. Crick, Leslie Barnett, and Drs. S. Brenner and R. J. Watts-Tobin of Cambridge University.

The picture of the code they favor is essentially this. It is a triplet, nonoverlapping code that reads out by starting at a fixed point and following the base groupings in one direction along the nucleic acid molecule.

SEQUENCE IS PREDICTED

Thus, if the sequence of bases were "UUU-UUA-AAU-UUU," the sequence of amino acids would be, according to the New York University and NIH findings, "phenylaline, isoleucine, asparagine, phenylalanine."

An overlapping code, which has been proved impossible, would have produced, "phenylaline, phenylaline, isoleucine, isoleucine, asparagine, asparagine, isoleucine, phenylaline, phenylalanine."

Dr. Crick's group produced experimental support for this triplet type of code with viruses that infect bacteria. They treated the viruses with certain chemicals that are believed to alter the base sequence of nucleic acids constituting the viral genes, by either adding or deleting a base at a time.

Those changes show up as mutations, alterations in the ability of offspring of the treated viruses to infect certain bacteria.

They found that the addition of one or two bases to a certain section of the virus' nucleic acid that controls that ability destroyed the function. Adding three bases to that section, however, restored the virus' infectivity for the particular bacterium.

The scientists interpreted this to mean that one base inserted in the nucleic acid threw off the message in the sequence of bases by one place in all that followed the adddition. Addition of the second base threw off the message two places. The third base, however, moved the message ahead three places—the length of a whole amino acid code "word"—thereby restoring the meaning, which was to make the specific protein that would allow the virus to infect the test bacterium.

TRIPLET IS INDICATED

This would happen, Dr. Crick noted, only if the coding ratio was three bases to one amino acid, or, less likely, a multiple of 3 to 1. Therefore, the Cambridge scientists reasoned, the code is probably triplet and "degenerate," meaning that an amino acid might be coded by more than one base triplet. Both the NIH and New York University groups have found evidence for this.

The problem remains, however, to determine the precise sequence of bases in each triplet for every amino acid and to ascertain that the code is, indeed, triplet in form. This might be achieved by statistical juggling and trial-and-error techniques applied to experiments such as those done by the NIH and New York University groups.

The possibility of accomplishing both of those tasks more directly—the hard way—was reported at the Indiana meeting by Dr. Seymour Benzer of Purdue University.

With techniques he developed, and which were used by the Cambridge group to find the basic form of the code, Dr. Benzer has mapped individual genes in a bacterial virus.

CISTRONS ARE LOCATED

That is, he determined the location of about 400 places on two sections of viral DNA, called cistrons, which control the virus' ability to infect a certain bacterium. Each spot represents a pair of bases, a rung in the DNA ladder.

The Purdue scientist noted that certain chemicals were known to cause mutations in the virus by specifically affecting one or another kind of base in the DNA. Knowing the location of each mutation so created—from his gene map—and the kind of bases that the chemicals specifically affect has enabled him to specify the precise base pairings at several locations along the viral nucleic acid.

What he wants to do now, and believes he can do, is to find chemicals that specifically affect other bases in nucleic acid and then to isolate the protein whose synthesis is directed by the cistrons within the viral DNA he has mapped.

By analyzing the protein's amino acid sequence and comparing it with the order of the DNA bases, it will be possible to determine directly, unequivocally and precisely what the genetic code is.

With that done, to borrow a line from an article by Dr. Hurwitz in the current Scientific American:

"The dream of the gene has become the reality of the protein."

TRANSPLANTATION OF TISSUES AND ORGANS

Mr. Fogarty. All right, what about transplantation of organs and other tissues? Is that important?

Dr. Hunt. Yes. This is a very important problem which has genetic connotations on one side and very important clinical connotations on the other. There is a great deal of interest in it.

Mr. Fogarty. What do you mean by a clinical connotation?

Dr. Hunt. The transplantation of tissues is——

Mr. Fogarty. You are talking about the transplantation of skin now?

Dr. Hunt. Transplantation of skin, and also functioning organs. There have been kidneys transplanted from one identical twin to another. But at the moment, if a person has both kidneys so badly damaged that he cannot survive, nothing can be done for him unless he has an identical twin who is willing to give up a kidney.

If we could elucidate the problems and get at the causes of——

GENETIC PROBLEMS OF TRANSPLANTING

Mr. Fogarty. Your biggest problem in the transplantation of organs and other tissues is the body rejecting this?

Dr. Hunt. Yes, this is the genetic part of it. Each individual has his own set of genes and enzymes, which are related to genes, and, as a result—for what exact reason we do not know, but we are quite sure it is related to the genes—the result is that a tissue transplanted from one person to another will not ordinarily survive unless the two people are identical twins, who have developed from the same fertilized ovum. In that case, you can transplant from one to the other. This is what makes us think it is a genetically determined activity or a situation.

Getting at this, to try to do something about it clinically so that burned people can have skin grafts from other people and have them take permanently, involves finding out what the genetic situation really is, and this is very complex. But work is being started on it.

Mr. Fogarty. Is this done in just two or three areas of the country?

Dr. Hunt. Well, I would say that anyplace where they are studying genetics, and many places where they are studying biochemistry in depth, are approaching or at least skirting the edges of this problem. So it is very hard to give a straight answer to your question.

Mr. Fogarty. Mr. Denton.

PRIMATE COLONIES

Mr. Denton. How many primate colonies do you have now?

Dr. Hunt. Two, I believe.

Dr. Shannon. Well, there is one in being.

Mr. Denton. That is the one in Puerto Rico?

Dr. Shannon. Well, I had in mind the grant program. The one in being is at the University of Oregon. There really is no formal primate colony in Puerto Rico. There is an island that runs a free-range colony of about 300 monkeys. And as an offshoot of that, there is a laboratory run by the Neurological Diseases and Blindness Institute.

Mr. Denton. There are three, then, in Puerto Rico—three colonies?

Dr. Shannon. There is one island for free range. There is one laboratory run in relation to the island, and there is an operation at the University of Oregon. These are the only ones in active operation at the present time.

Mr. Fogarty. They have two more islands that they have leased for future use.

Mr. Denton. But they have not gotten monkeys on them yet?

Dr. Shannon. No, sir.

MONKEYS FOR VACCINE EXPERIMENTS

Mr. Denton. These are monkeys that you use for vaccination for measles?

Dr. Shannon. Yes, sir.

Mr. Denton. Where do they keep them?

Dr. Shannon. Well, sir, the only specialized monkeys that we have had for the vaccine studies in measles came from Puerto Rico, and were completely isolated from human contact and maintained in isolation in Bethesda.

Mr. Denton. Here?

Dr. Shannon. As caged animals; yes, sir.

Mr. Denton. Now, do those monkeys get measles?

Dr. Shannon. If they have extensive human contact, yes.

Put it this way: They develop measles antibody in the blood, which means they have had a measles exposure.

Mr. Denton. And the monkeys you have, you have to keep isolated?

Dr. Shannon. Yes, sir.

Mr. Denton. Now, do you do intramural research in this branch of our general research out at Bethesda?

Dr. Shannon. We do not, sir.

Mr. Denton. It is all by grants?

Dr. Shannon. Yes, sir.

EXPENDITURES FOR APPROVED GRANTS

Mr. Denton. Now, of the $124,600,000 that you had last year, how much of that has been for grants?

Dr. Shannon. I can give you the breakdown.

Mr. Denton. All right.

Dr. Shannon. And this will have been expended by the end of the next 4 months.

Dr. Hunt. We will utilize the full amount available.

Mr. Denton. All right.

PROCEDURE FOR APPROVING APPLICATIONS FOR GRANTS

Now, who passes on these projects to decide if you will make a grant?

Dr. Hunt. We use the regular study section-council mechanism for this program as for the other Institutes. The Council which passes on grants made by the Division of General Medical Sciences is the National Advisory Health Council.

Mr. DENTON. Are these doctors?

Dr. HUNT. About half of them are M.D.'s. At least half are scientists.

LIST OF NATIONAL ADVISORY COUNCIL MEMBERS

Mr. DENTON. Will it be possible to put their names and identification in the record?

Dr. SHANNON. Yes, sir; we should be glad to.

Mr. DENTON. I think that would be good.

(The requested information follows:)

NATIONAL ADVISORY ALLERGY AND INFECTIOUS DISEASES COUNCIL

Dr. Francis S. Cheever (64), dean, School of Medicine, University of Pittsburgh, Pittsburgh, Pa.

Mr. David C. Crockett (65), associate director, Massachusetts General Hospital, 274 Charles Street, Boston, Mass.

Dr. Harry F. Dowling (64), head, Department of Medicine, University of Illinois, Chicago, Ill.

Dr. William W. Frye (63), dean, School of Medicine, Louisiana State University, New Orleans, La.

Mrs. Irene F. McCabe (64), 1342 McCutcheon Road, Richmond Heights, Mo.

Dr. Walsh McDermott (65), professor of public health and preventative medicine, Cornell University Medical College, 1300 York Avenue, New York N.Y.

Dr. Gordon Meiklejohn (62), head, Department of Medicine, University of Colorado Medical Center, 4200 East Ninth Avenue, Denver, Colo.

Mr. Hamilton S. Putnam (63), 18 School Street, Concord, N.H.

Dr. William B. Sherman (63), associate clinical professor, Columbia University, 60 East 58th Street, New York, N.Y.

Dr. Charles E. Smith (62), dean, School of Public Health, University of California, Berkeley, Calif.

Dr. Laurence H. Snyder (65), president, University of Hawaii, Honolulu, Hawaii.

Dr. W. Barry Wood, Jr. (62), head, Department of Microbiology, the Johns Hopkins University School of Medicine, 601 North Broadway, Baltimore, Md.

EX OFFICIO MEMBERS

Dr. Robert C. McClaughry (VA), Director, Educational Services, Department of Medicine and Surgery, Veterans' Administration, Washington, D.C.

Alternate for:

Dr. William S. Middleton, Chief Medical Director, Department of Medicine and Surgery, Veterans' Administration, Washington, D.C.

Capt. James R. Kingston (Navy), Bureau of Medicine and Surgery, Potomac Annex, Washington, D.C.

Alternate for:

Dr. Frank B. Berry, Deputy Assistant Secretary (Health and Medical), Office of Assistant Secretary of Defense for Manpower, Department of Defense, Washington, D.C.

Dr. Luther L. Terry (Chairman), Surgeon General, Public Health Service, Washington, D.C.

NATIONAL ADVISORY ARTHRITIS AND METABOLIC DISEASES COUNCIL

Dr. Charles H. Burnett (62), professor of medicine, School of Medicine, University of North Carolina, Chapel Hill, N.C.

Dr. Vincent du Vigneaud (64), professor of biochemistry, Cornell University Medical College, 1300 York Avenue, New York, N.Y.

Dr. Conrad A. Elvehjem (65), president, University of Wisconsin, Madison, Wis.

Dr. Clifford M. Hardin (64), Chancellor, University of Nebraska, Lincoln, Nebr.

Dr. Franz J. Ingelfinger (65), professor of medicine, Boston University School of Medicine, Massachusetts Memorial Hospitals, 750 Harrison Avenue, Boston, Mass.

Mr. Frederick M. Lange (64), executive vice president, Dallas Community Chest trust fund, 420 South Akard Street, Dallas, Tex.

Dr. John S. Lawrence (63), professor and chairman, department of medicine, University of California Medical Center, Los Angeles, Calif.

Dr. Arnold Lazarow (65), professor and head, Department of Anatomy, University of Minnesota Medical School, Minneapolis, Minn.

Mrs. Florence S. Mahoney (63), 3600 Prospect Avenue NW., Washington, D.C.

Dr. Carl V. Moore (62), professor of medicine, Washington University School of Medicine, 600 South Kingshighway, St. Louis, Mo.

Mr. Eugene S. Pulliam, Jr. (63), managing editor, Indianapolis News, Indianapolis, Ind.

Dr. Charles Ragan (62), director, First Medical Division, Bellevue Hospital, 462 First Avenue, New York, N.Y.

EX OFFICIO MEMBERS

Dr. Solomon A. Berson, Chief, Radioisotope Service, Veterans' Administration hospital, 130 West Kingsbridge Road, Bronx, N.Y.

Alternate for:

Dr. William S. Middleton, Chief Medical Director, Department of Medicine and Surgery, Veterans' Administration, Washington, D.C.

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Mr. Mike Gorman (65), executive director, National Committee Against Mental Illness, 1028 Connecticut Avenue N.W., Washington, D.C.

Dr. George C. Ham (65), professor and chairman, Department of Psychiatry, University of North Carolina, Chapel Hill, N.C.

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Dr. George A. Wolf, Jr. (62), executive director and vice president for medical affairs, Tufts New England Medical Center, Boston, Mass.

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Dr. Harve Carlson, National Science Foundation, Washington, D.C.
Dr. Luther L. Terry (Chairman), Surgean General, Public Health Service, Washington, D.C.

PROCEDURE FOR APPROVING APPLICATIONS FOR GRANTS

Dr. SHANNON. Could I give you the background of how the total grant activity operates?

Mr. DENTON. Yes.

Dr. SHANNON. A grant application is received by our Division of Research Grants and is appraised by the staff of the Division to determine for what general program area it is most suitable. The application then goes to a technical advisory group, called a study section, that determines its scientific worth without regard to funds available for payment and without regard to the particular program that it will be fitted into.

If it is approved at that stage, it is then referred to one of the advisory councils such as the National Advisory Health Council, or the National Cancer Council. The Council determines whether this approved application is suitable for support from the funds of its particular Institute—whether it is in line with the programs that are being supported by the Institute. If they approve it, they recommend its approval by the Surgeon General, who must approve it specifically before it is paid.

Actually, the Surgeon General delegates the latter approval to the Director of the Institute.

There are thus four steps: assignment to an area, technical review, policy review, and payment.

Mr. DENTON. All the work is done by the staff of the NIH except for this Council that passes on it?

Dr. SHANNON. No, sir. The study section that gives the technical review also is composed of outside advisers.

Mr. DENTON. Are they doctors and scientists?

Dr. SHANNON. They are all scientists.

METHOD OF RATING PROJECTS

Mr. DENTON. Do you rate projects like 1, 2, 3, 4, A, B, C, or something like that?

Dr. SHANNON. At the study section level they are rated.

First, may I say they are approved or disapproved. The approved projects are then rated.

They are rated 1 to 5; then these ratings are added up and multiplied by 100 and then divided by the number of raters so you get a priority system in which the highest score is 100. If it is approved, the lowest priority would be 500.

ADEQUACY OF THE PRESIDENT'S BUDGET FOR RESEARCH GRANTS

Mr. DENTON. In the President's budget this year, we have $147,826,000. Now how many of projects 1, 2, 3, 4, and 5 will that take care of?

Dr. HUNT. The projects come to the Council with a number, which ranges from 100 down into the 150's, 200, 250, and so on.

Mr. DENTON. I thought Dr. Shannon said they went 1 to 5.

Dr. HUNT. The individual rater at the study section meeting rates from 1 to 5. Those are then averaged and multiplied by 100.

Dr. SHANNON. To give a whole figure.

Dr. HUNT. So that the project comes out of the study section with a rating which may be 237.

Mr. DENTON. It may be what?

Dr. HUNT. It may be 237 or 196 or any other three-digit number.

Dr. TERRY. It ranges from 100 to 500.

Mr. FOGARTY. It does not mean that if that project has a 500 rating, it might not be one of the best. You have had some good leads from projects with a 500 rating, have you not?

Dr. SHANNON. Yes.

Could I make a general statement, sir?

Mr. DENTON. Yes.

Dr. SHANNON. On balance, the projects with the low priority numbers; that is, 100 to 200, will in general be the best; on balance.

Mr. DENTON. The low numbers will be the best?

Dr. SHANNON. On balance, the ones with the highest priority numbers will be the poorer projects.

But first, all of them, prior to any rating, must be approved as worthwhile. It is, of course, very difficult to look at an individual project and make a prediction over a 5-year or 10-year period as to how effective the information that will be derived from the project will be or to what extent it may modify the course of science.

Now, Dr. Hunt's appropriation will pay down, as best I can guess looking at the figures here, to a priority rating of about 350 depending upon——

Mr. DENTON. And how much money will be used for that?

Dr. SHANNON. Of the total budget of $147 million, $100 million is for research projects.

Mr. DENTON. That $100 million will take your projects down to about 350?

Dr. SHANNON. 350, yes.

APPROVED UNFUNDED PROJECTS

Mr. DENTON. How many projects below that do you have that have been approved and that you do not have enough money to grant?

Dr. HUNT. We expect that there will be about $5 million worth of approved, unpaid projects at the end of next fiscal year, a year from June.

Mr. KELLY. About 222 unpaid projects.

Mr. DENTON. I think that is all.

RETIREMENT OF DR. HUNT

Mr. FOGARTY. Dr. Hunt, is there anything else you would like to say?

Dr. HUNT. Only that I have appreciated working with this committee for the past many years.

Dr. SHANNON. Mr. Fogarty, I would like to take note at this time that this is Dr. Hunt's last appearance before you.

Mr. FOGARTY. Well, we are sorry to hear that. I did not know that, Doctor. Where are you going?

Dr. HUNT. I will be retiring from active duty on April 1 and going with the Educational Council for Foreign Medical Graduates.

Mr. FOGARTY. Is that what you wanted to do? I thought you might be with that new medical school at Brown.

Dr. HUNT. I was not asked.

Dr. SHANNON. We are very sorry to lose Dr. Hunt.

Mr. FOGARTY. Well, we have seen you on quite a few jobs in 16 years, have we not?

Dr. HUNT. Yes, sir.

Mr. FOGARTY. I think you have done a really excellent job, and you have always been honest and aboveboard with the committee.

Dr. HUNT. Thank you, sir.

Mr. FOGARTY. I think you have done a great service for the country.

Dr. TERRY. How many years of service do you have, Dr. Hunt?

Dr. HUNT. It was 25 years last July. It will be just short of 26 when I leave.

Dr. TERRY. I just wanted to be sure that you understood that he was not just putting in 16 years.

Mr. FOGARTY. Thank you very much, Doctor.

Dr. HUNT. Thank you.

(The following was submitted at the request of the committee:)

HIGHLIGHTS OF RESEARCH PROGRESS IN GENERAL MEDICAL SCIENCES, 1961

RESEARCH IN BIOLOGY

BASIC EVENTS IN CELL REPRODUCTION CAN OCCUR INDEPENDENTLY

The earliest definable event in the sequence of mitosis is the duplication of cell centers (centrioles), following which the sister centers separate to form the poles of the dividing cell. Coordinated with this is the synthesis of genetic DNA (deoxyribonucleic acid), duplication of the chromosomes and movement of sister chromosomes to the sister centers.

Daniel Mazia and coworkers have shown in experiments on dividing sea urchin eggs that DNA synthesis is initiated entirely independently of cell center duplication, and that processes of reproduction and division of the centers themselves are separable from one another.

Some sort of machinery must exist to integrate the controlling factors in cell reproduction into the coordinated process which is known to occur, the investigators suggest. The idea that the first event—cell center duplication—is an initiating step which triggers DNA synthesis and places interdependent steps in the time sequence of mitosis has been an extremely attractive hypothesis. Mazia's group finds this theory untenable, in the light of their experiments.

The findings, and the experimental method for separating the mitotic events in the sea urchin, were published in The Journal of Biophysical and Biochemical Cytology and in Experimental Cell Research. Nancy Bucher, Patricia Harris, and Thomas Bibring contributed to the work, which is reported from the University of California, Berkeley and La Jolla, California; and Harvard University, Boston, Massachusetts. DGMS research grants support these studies.

A REVIEW OF THE HUMAN CHROMOSOMAL ABNORMALITIES REFLECTED IN VARIOUS DISEASES

Scientific interest in congenital abnormalities has increased markedly since the development of methods for culturing and preparing human body cells so that their chromosomes can be studied. This work led in 1956 to the discovery that normal body cells have 46 chromosomes which can be arranged in seven groups, photographed, and numbered so various investigators can compare their findings with those of other people and each can identify what the other is describing.

Since 1956, numerous people have reported findings of abnormal looking chromosomes, or abnormal numbers of chromosomes within body cells, or even of conditions in which some cells in some tissues appear normal and others have abnormal chromosome arrangements—a condition called mosaicism. These unusual physical structures in the genetic apparatus of body cells have been found closely correlated with unusual mental and physical conditions of the body as a whole. More and more investigators are taking small samples of several tissues from available members of the families of such abnormal people and trying to learn from such studies how these defects arise and are inherited.

Because much of the information is recently acquired, and the communication of it has been widely scattered in time and organ of publication, a review, such as this, of the relations of peculiar chromosomes to mental, to sexual, and to other physical abnormalities, and also to the occurrence of leukemia, represents a meaningful and useful synthesis of biologic and medical information. O. J. Miller, of Columbia University College of Physicians and Surgeons, New York City, and H. L. Cooper and Kurt Hirschhorn, of the New York University Medical Center, New York City, have now published such a review in Eugenics Quarterly entitled, "Recent Developments in Human Cytogenetics." The work was supported by a grant from the Division of General Medical Sciences.

CELLS OF HIGHER PLANTS GROWN AS SUSPENSIONS IN SYNTHETIC CULTURE MEDIA

John G. Torrey and Jakob Reinert at the Institute for Cancer Research in Philadelphia, Pennsylvania, have observed that tissue cells from roots of typical flowering plants can be cultured as single isolated cells in suspension in chemically defined and completely artificial environments.

These synthetic culture media may be potent tools for enlarging man's knowledge of organization and disorganization as expressed in physicochemical activities of individual cell behavior.

Preliminary use of this research tool on cells from carrot and bindweed showed a direct relationship between increasing amounts of auxin (a plant growth regulator) in the culture medium and the tendency for organized groups of cells (tissues) to become separated into actively-dividing isolated single cells scattered throughout the culture. Auxin is called a growth regulator because it promotes the natural capacity in plant cells to enlarge, to undergo cell division, and to differentiate into various tissues with specific functions. Vitamins, including several B vitamins, were also involved in the different requirements for individual cell versus cooperative or tissue, type of cell living.

Descriptions of the new culture technique, and observations on auxin and vitamin requirements of the cells are published in Plant Physiology. The work was supported by a grant from the Division of General Medical Sciences.

LONGITUDINAL STUDY OF SKELETAL MATURATION IN CHILDREN

As part of a larger project in child research, Charlotte F. Hansman and Marion M. Maresh of the University of Colorado in Denver have reported two facets of the work which were supported by DGMS. The first concerns wide differences in bone development as seen in X-ray photography of the wrist. Hansman and Maresh report that in infancy, bone and chronological age coincide. In childhood, wrist bones generally develop sooner in girls than in boys by about 3 years; but perfectly normal, well-fed children may show such differences between chronological age and bone age that the phrase "retarded bone age" should carry no stigma. By the time they are about 16, all the children will show a degree of ossification again comparable to the chronological age.

The second aspect of this skeletal study concerns the patterns of relationship between chronological age, skeletal age, and the onset of the physical characteristics of adolescence. Children whose bone age is consistently over 12 months above the median mature early, those consistently over 12 months below the median mature later. Of the middle group about one-third of the girls and a smaller proportion of boys show a lag in bone age, but they catch up at adolescence.

The studies were published in the American Journal of Diseases of Children.

BASIC DATA ON BLOOD AND BODY FLUIDS PUBLISHED IN HANDBOOK FORM

Philip L. Altman and coworkers of the Committee on Biological Handbooks of the Federation of American Societies for Experimental Biology in Washington, D.C., have published Blood and Other Body Fluids (1961). This is a sourcebook of tables expressing basic established data of interest to biologists and to physicians.

The first 12 chapters deal with physical properties and chemical composition of blood in man and in animals. There are sections devoted to electrolytes, nitrogenous substances, lipids, enzymes, blood cells, oxygen dissociation, acid-base balance, blood groups, etc.

The remaining 13 chapters deal with the hemolymph of insects, and with cerebrospinal fluid, liquid content of nerves, fluids of body cavities, body water, urine, digestive reproductive and dermal secretions, milk, and the fluids of ear and eye in man and in animals.

There are source and bibliographical citations with each table, an appendix with conversion formulae and regression equations, and an index to make the volume a useable and valuable sourcebook. DGMS, the National Science Foundation, and the U.S. Air Force have all contributed to the production of this handbook.

SYMPOSIUM ON THE PATTERNS OF ORGANIZATION OF MACROMOLECULAR COMPLEXES, AND THEIR EFFECTS ON LIFE PROCESSES

Macromolecular Complexes (M. V. Edds, Jr., editor, Ronald Press Company, New York, 1961) is the sixth annual symposium publication of the Society of General Physiologists. The symposium in the field of morphogenesis (origin of form) was held at the University of Illinois, and was supported by DGMS. It resulted in nine unusual papers on research in the realm of pure or basic science at the physicochemical level.

One complex but unified subject covered is the structure of the water in the spaces between a network of protein molecules within a cell, the thermodynamics of interactions likely to produce short range structural alignments as typified in insulin fibrils and casein micelles, long range alignments as seen in platelets, tobacco mosaic, and chromosome pairing, and the formation of energy barriers to prevent local penetration of water molecules within areas of a cell.

The structural basis for the induction of mineralization of collagen to form teeth and bones—an intracellular process involving the reactions of supersaturated (metastable) calcium phosphate solution with special sites on native-type collagen fibrils is discussed. The protein molecules of the fibrils are apparently so arranged that these sites fit perfectly with parts of molecules in the solution and hence act like crystals. They start to grow using much the same process involved in the production of raindrops from water in supersaturated air by seeding clouds with silver iodide.

The chapter on the construction of chloroplasts (bodies containing the green pigment in plants) points out that chloroplastin has the properties of a liquid crystal. These properties probably account for the lamellar (thin-layered) structure and for the orientation of the pigment complex within the chloroplast. Another chapter about the structure of the chromatophores (minute pigment bodies) of photosynthetic bacteria, suggests that these bodies are built up from smaller identical units arranged so that there is twice as much surface area of the protein parts as there is of the lipid-protein interface.

One article explains that quick freezing to extremely low temperatures has enabled the investigator to compare the lamellar systems of structure in nerve sheath (myelin) with that in parts of the retina. He feels that the lamellar structure, with its shifting electrical charges at the water-lipo-protein interfaces, is perhaps responsible for the liquid crystal conditions found in both. He suggests that "fluid crystal elements are the true 'energy transducers of life.' "

A discussion of polysaccharide-protein complexes of yeast cell walls indicates that the wall is composed of glucan, manan, chitin, and some protein forming a most insoluble structure apparently held by disulfide bonds. When the yeast forms new cells, the bonding seems to loosen and in about 30 seconds the wall appears to blow out and the cell contents pop through the circular hole to form a bud. The new wall grows from the parent cell along the out-blown fibrils.

In cell walls of green plants, the cellulose apparently contains other sugars than the glucose known to be present, and the microstructure (somewhat like that of collagen in animals) appears to be a folded lattice. The cellulose and protein seem to be in a relationship similar to that found in animal skin, though in plants the microfibrils apparently have a core of cellulose and an outer sheath of protein, whereas in animals the reverse is true. In plants, the microfibrils are laid down following cytoplasmic orientation, and in close contact with the cytoplasm. They grow by end synthesis. Later, the protein seems to leave the macromolecular complex to take up a new alignment and to form a new cellulose layer on the inside of the old, starting from the ends of the old microfibrils—hence the basketlike interwoven structure of cell walls.

SYMPOSIUM ON METHODOLOGY IN BASIC GENETICS

The third symposium on methodology in basic genetics was held at the University of Texas, Austin, on May 3, 4, and 5, 1961. The meeting was sponsored by the Genetics Study Section of the National Institutes of Health, under a grant from the Division of General Medical Sciences. Dr. Walter J. Burdette of the University of Utah College of Medicine, Salt Lake City, served as principal investigator under the grant.

More than 18 papers were presented covering such topics as induced and spontaneous mutations, and the recombination of bacteriophage; mutation and population genetics, transformation, transduction, and conjugation of bacteria; meiotic recombination, conversion, and mitotic recombination of fungi; and mutation, pseudoalleles and recombination in Drosophila. Also included were papers on gene-protein relationships in viruses, bacteria and fungi; and cytoplasmic inheritance in fungi and protozoa. The proceedings are to be recorded in a volume to be published for investigators in the biological sciences, and it is expected that the volumes covering the symposia will serve as source books of genetics methodology.

The first symposium, held at the University of Utah, in May 1960, dealt with human genetics, and the second symposium, held at the Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine, in September 1960, was on mammalian genetics.

FIRST MEETING OF THE AMERICAN SOCIETY FOR CELL BIOLOGY

The first meeting of the newly formed American Society for Cell Biology was held at the Edgewater Beach Hotel, Chicago, Illinois, on November 2, 3, and 4, 1961. Specific purposes of the Society are to further research in cell biology as broadly interpreted, and to facilitate interdisciplinary communication among cell biologists. Three symposia were organized around interdisciplinary concepts designed to attract scientists from diverse areas of cell biology. The Division of General Medical Sciences assisted in supporting the costs of the symposia.

GUIDE TO LITERATURE ON LABORATORY ANIMALS

Jules Cass and coworkers at the University of California have completed an annotated bibliography on laboratory animals which brings together previously scattered and hidden publications concerning procurement, maintenance, and use, as well as the intrinsic characteristics, of the representative species used for scientific and medical research.

The bibliography appears as Supplement 6 of the December 1960 Federation Proceedings, published by the Federation of American Societies for Experimental Biology and Medicine. The issue is entitled "A Guide to Production, Care and Use of Laboratory Animals." Coauthors are Irene Campbell and Lilli Lange.

Of its nine chapters, the first emphasizes basic scientific resource lierature pertaining to the biology of the laboratory species themselves. The references in chapters 2, 3, and 7 focus more on standard techniques and circumstances for therapeutic, experimental, and nutritional intervention in, and control of, normal and abnormal life processes. The other chapters concern institutional sources, standards, environments; and techniques and facilities for systematic, legal, and efficient procurement and maintenance of the animals.

Thus the publication should help satisfy the information retrieval needs which are widespread among research personnel who depend on laboratory animals for their progress; both those who are concerned with the states of biological organization and disorganization that occur naturally in living systems, and those who are concerned with the social implications and useful modification of such states, such as research clinicians and administrators.

APPLICATION OF FETAL ECG TECHNIQUES TO ANIMALS WILL AID HUMAN STUDIES

Over the past 3 years, Saul D. Larks and coworkers at the University of California developed techniques for recording the fetal electrocardiograph (F–ECG) which are applicable to the diagnosis of multiple pregnancies and heart defects in the human fetus.

The California group reported the adaptation of these techniques to large domestic animals. Data were presented in The Cornell Veterinarian, showing that the F–ECG can be recorded in the mare and the cow with consistent accuracy and relative ease.

Animal F–ECG recording makes available information on fetal number and well-being, useful for animal husbandry and veterinary medicine, Larks suggested. The application to animals also affords an investment in future experimental data pertaining to human biomedical problems, such as drug effects on the fetal heart and placental-fetal relationships. The complementary relationship between research approaches to nonhuman and human life forms is axiomatic in the life sciences.

Louis W. Holm and Harold R. Parker coauthored the study in animals, which is reported from the University of California in Los Angeles, and Davis, California. DGMS grants supported the work.

CONTRIBUTIONS OF VETERINARY MEDICINE TO HUMAN HEALTH

H. E. Miller, as managing editor, has published a book, Comparative Medicine in Transition (Lord Baltimore Press, 1960), containing the proceedings of the First Institute of Veterinary Public Health Practice which was presented by the School of Public Health of the University of Michigan at Ann Arbor, Michigan. Publication of the proceedings was supported in part of DGMS. The Institute was designed to explore and document contributions of veteraninarians to human health, to evaluate present veterinary public health practices and administration, and to publish such findings and suggestions as reflected the thinking of the Institute in hopes of providing both a source book for future study and a stimulus to further interdisciplinary cooperation between workers in the human and animal aspects of medicine, especially in public health.

RESEARCH TRAINING CONFERENCE IN VETERINARY AND COMPARATIVE PATHOLOGY

A DGMS-supported conference on research training in veterinary and comparative pathology in various institutions was held at Portsmouth, New Hampshire, in October to discuss the theoretical and practical aspects of research training in the total field of pathology. The meeting (sponsored by the Pathology Training Committee of the Division of General Medical Sciences, NIH), was attended by committee members and invited representatives of several disciplines, including veterinary pathologists, comparative pathologists, medical pathologists, and other scientists with an interest in, or a viewpoint on, research training in these fields.

The discussions ranged from recruitment of research personnel to training for professional service, for teaching, and for research. One session considered opportunities for careers in research in veterinary and comparative pathology. The proceedings were recorded and the report is to be published.

IMPORTANT PHASE OF MAMMALIAN REPRODUCTION STUDIED IN RATS

Previous work with humans, sheep, rabbits, and mice has suggested that there is a critical stage in the survival of the mammalian embryo several days after mating. In two articles in the Journal of Reproduction and Fertility, R. W. Noyes and Z. Dickmann of Stanford University, Palo Alto, California, reported that experiments with rats show that this occurs late on the fifth day.

Moreover, by transplanting fertilized ova of different ages into the uteri of rats at various ages of pseudopregnancy, these DGMS grantees demonstrated that any ova younger than the pseudopregnancy were usually destroyed the first 2 days or early on the fifth day, but ova 1 day older often delayed development until the uterus was ready late on the fifth day and then implanted and formed a fetus larger than usual.

However, neither a fourth nor a fifth day egg would implant in the uterus of a fourth day pseudopregnant rat. The early part of the fifth day the uterus appears to be antagonistic to all incompatibly aged ova, and after the sixth day, ova do not implant. Successful offspring usually come from eggs which reach the uterus at just the right time—the afternoon of the fifth day after mating.

The authors believe that further study of these uterine-ovarian relationships will clarify our understanding of one of the most important phases of mammalian reproduction.

FASTER TURNOVER OF MUSCLE PROTEINS IN MICE WITH MUSCULAR DYSTROPHY

Comparing the turnover of muscle proteins in normal mice and mice with congenital muscular dystrophy, DGMS grantees at the Hôspital des Enfants Malades, in Paris, found a faster turnover both of water extractable proteins in the dystrophic mice and of the normally stable myosin.

Whether these accelerated rates are due to a shorter life span of the dystrophic muscle cells or to an abnormal molecular turnover is not certain but the latter seems more probable.

It would be important, the authors feel, to know whether the same abnormality occurs in human muscular dystrophy.

Drs. Jacques Kruh, Jean-Claude Dreyfus, Georges Schapira, and George O. Gey, Jr. reported their findings in The Journal of Clinical Investigation.

VASOPRESSIN PRESENTED AS AGENT OF INTERACTION BETWEEN CENTRAL NERVOUS AND PERIPHERAL VASCULAR STRUCTURES

Seth K. Sharpless and Alan B. Rothballer of the Albert Einstein College of Medicine in New York City, used classic autopharmacologic techniques in cats (encéphale isolé preparations) in an attempt to detect the release of catecholamines from the brain during experimental stimulation of its reticular activating system. There is an abundance of catecholamines in the brain stem, and the idea that reticular activation and the associated excitation of arterial constriction (pressor response) might involve their release from the brain has been winning increasing support.

Sharpless and Rothballer report that the pressor substance released when the reticular formation was electrically stimulated in the cat was not a catecholamine, but probably vasopressin, and that a relatively distinct tract of fibers passing through the midbrain exerts a potential control over the hypothalamic-pituitary system in this connection.

In the course of 40 cat preparations, elaborate precautions were taken to eliminate the possibility that pressor amines, released peripherally via cranial or spinal nerve pathways, might be causing the rise in blood pressure. In the framework of these precautions, the investigators compared the systemic response to reticular stimulation with the response to a wide variety of pharmacologic agents (including the catecholamines) which also affect blood pressure. They found the responses to reticular activation matched most closely the effects of injected vasopresin, in the patterns of blood pressure fluctuation, and other details such as movement of the denervated nictitating membrane. Hence they concluded provisionally that the pituitary pressor factor, released from the head, is the chemical mediator of the neuro-vascular response of arterial constriction which occurs on activation of the reticular formation in the midbrain. Their findings do not rule out a humoral role for amines released from cells in the vicinity of the reticular synapses, since circulation of these chemicals could be confined to the brain itself by the blood-brain barrier.

In attempting the extremely delicate task of mapping, through use of electrodes, the excitatory region of the reticular part of the brain, the investigators gained some information about the location in the midbrain of the nerve pathways projecting to the pituitary, hypothalamus and other cranial structures for conduction of the reflexes by which the organism coordinates this secretory activity. They suggested that the significance of this mechanism for individual adaptation to environment (its importance to the overall economy of an organism) will be found in the long recognized fact that an antidiuretic pressor substance is released during pain and emotional excitement.

The details of the autopharmacological device they used, and the outlines of the biological mechanism thus mapped, appeared in the American Journal of Physiology.

Vasopressin not only increases blood pressure by prompting constriction of arteries, but also increases blood volume by prompting reabsorption of urinary water from the renal tubules into the circulation—the antidiuretic effect. Recent summaries of evidence indicate that vasopressin reduces coronary circulation, occasionally to the extent of cardiac distress.

The reticular formation of the brain stem, according to current literature, appears to mediate the expression by mammals of many of the inherent patterns of whole body adjustment to environmental space, or individual behavior. Such patterns of spatial orientation as posture, stretch, and locomotion seem to depend either wholly or in some parts (myoskeletal and vascular reflexes) on the activity of the reticular nerve cells. The reticular formation is, in turn, regulated by impulses from the higher (cerebral and cerebellar) brain structures through which the individual organizes perceptual responses to spatial tolerance.

RESEARCH IN THE CHEMISTRY OF LIFE PROCESSES

NEW LIGHT IS SHED ON THE CHEMICAL STRUCTURE OF ACTH

Choh Hao Li, Jonathan S. Dixon, and David Chung of the University of California at Berkeley reported in detail (Biochimica et Biophysica Acta, 1961) an amino acid sequence for bovine adrenocorticotropic hormone (ACTH) which is identical in composition, but not in arrangement, with the ACTH from sheep, and is also very similar to that from pigs. All the differences are found between positions 25 and 33 of the 39 total positions, and the inference has been drawn that there is an identical active core of the compound which produces identical ACTH activity. This is similar to the general findings in the case of insulin, in which the differences found btween different animals are slight but important, since people can tolerate insulin from one animal better than from another.

Li and Dixon also reported in 1960 (Journal of the American Chemical Society, 82, September) that they have extracted a melanocyte-stimulating hormone from horses which is identical with that from cattle and pigs.

Dr. Li and his team are DGMS-supported, but other workers, among them, Dr. Klaus Hofmann at the University of Pittsburgh, Pittsburgh, Pennsylvania, are also working on the synthesis of ACTH. The National Institute of Arthritis and Metabolic Diseases is supporting Dr. Hofmann, and some of his work on synthesizing an ACTH molecule was published in Chemical and Engineering News in 1960.

EVIDENCE OF ENZYME REPRESSION IN HIGHER ANIMALS

The interest of biological scientists in many fields is focusing on the natural phenomenon of enzyme repression; with the proposal of theories explaining aspects of protein synthesis, antibody formation, tissue differentiation (organ formation), tissue dedifferentiation (neoplasm formation), drug effects, and the operation of memory units in the brain, in terms of this molecular metabolic control system.

Enzyme repression is known to govern certain metabolic systems in one-celled organisms by the principle of negative feed-back. Thus the end product (metabolite) of the sequence of enzymatic events, which constitutes a particular biosynthetic process, limits the concentration of the first enzyme in that sequence.

DGMS-grantee Leo Szilard recently proposed a general theory of enzyme repression in higher animals and showed (by mathematical models) that a system consisting of an enzyme, an enzyme-forming apparatus, and a repressor may exist in two stable states, providing the combining energy among the components of the system lies within certain limits. This theory of "paraconstitutive systems" has been referred to as one of the most important biological hypotheses made in recent times. Although Szilard's postulates assumed the operation of enzyme repressors in such basic life processes as protein synthesis and antibody formation in higher organisms, he acknowledged his lack of experimental evidence for their existence.

Clear-cut evidence that enzyme repression does occur in higher organisms (mammals and birds) was transmitted by DGMS-grantee James B. Walker in reports in 1959, 1960, and 1961. Repression of the enzyme, arginineglycine transamidinase, by dietary creative was achieved in rats, chickens, and ducks. Transamidinase is the first enzyme on the biosynthetic pathway that leads exclusively to creatine. Repression by creatine feeding resulted in levels of liver transamindinase activity as low as 2 percent of normal in the birds. When feeding was suspended entirely, the repression continued until a normal diet or a diet containing a sugar and a complete protein was fed. Diets lacking sugar or containing only incomplete protein failed to restore the activity. Treatment of the animals with an amino acid antimetabolite (ethionine) prevented recovery, even when a normal diet was fed.

Walker suggested that creatine repression may have survival value for birds by enabling them to conserve essential amino acids for protein synthesis. This speculation has some experimental substantiation.

From the experimental standpoint, he pointed out that his method for study of transamidinase repression affords a precise and useful tool for further inquiry into related enzymatic systems. He suggested that the steady-state transamidinase level of a diflerentiated tissue (organ) may reflect the repressor concentration of that tissue. He also speculated that tissue dedifferentiation (neoplastic growth) may result from disturbances of enzyme repressors which control tissue differentiation, an idea with stimulating potentialities for cancer research.

Of genetic interest is the fact that the experimental repression of liver transamidinase measured by Walker seems to mimic, physiologically, mutation of the genetic mechanism which controls this pathway of amino acid metabolism.

Walker reported from Baylor University College of Medicine, Houston, Texas. Szilard reported from the Enrico Fermi Institute for Nuclear Studies, University of Chicago, Chicago, Illinois. Walker's work was published in the Journal of Biological Chemistry (1960, 1961), and Biophysica et Biochimica Acta (1959); and Szilard's was in Proceedings of the National Academy of Sciences (1960).

DIFFERENTIAL SUSCEPTIBILITY OF SPERM AND SPERMATIDS TO IONIZING RADIATIONS

The natural patterns of spatial distribution of the chromosomal bodies relative to the caryolymph of the cell nucleus appear to play a role in the susceptibility of differentiating sperm cells to mutation. The mature sperm and its precursor, the spermatid, are known, from various experimental studies, to differ in mutation rate, on exposure to ionizing radiations, in various vertebrate and invertebrate animals. Also, the characteristic patterns of behavior, or spatial orientation, of these chromosomal masses have been well documented photographically. In sperm the condensed chromosomes are packed tightly together in the small spermheads, while the chromosomes of spermatids, located in regular nuclei, are separated from each other by some space within the caryolymph.

Combining this information in a report in the *American Naturalist*, Dr. Werner Schmid of the University of Texas, in Austin, with DGMS grant support, offered the suggestion that the spatial orientation of the chromosomal mass influences its vulnerability to radiation dosage. His hypothesis assumes that the diffusing secondary radiochemical products of ionizations, occurring in the immediate neighborhood of the chromosomes, cause a considerable amount of chromosomal damage in addition to the effects due to ionizations occurring within the structures of the chromosomes themselves. The additional space is present around the chromosomes of spermatids as in most other types of cells, but it is practically missing in the exceptional cell-type represented by sperm.

On the basis of this theory, it seems possible to explain not only the lesser sensitivity of sperm to X-rays but also their peculiar reaction to oxygen and neutrons.

TIME STUDIES OF AMINO ACID UPTAKE INDICATE NEUROSPORA TAKES BUT A FEW SECONDS TO MAKE A PROTEIN

M. Zalokar, formerly of Yale University and now of the University of California at La Jolla, working with intact living *Neurospora*, found the cells of this fungus actively took up radioactive proline from the surrounding medium at a rate proportional to the concentration of proline in the medium and dependent on the temperature. This process continued until the internal concentration was higher than that of the external supply. The proline was incorporated by the cells into proteins (insoluble in tricholoroacetic acid), slowly at first, and then at a constant linear rate.

Zalokar discusses the kinetics of his experiments and concludes that living *Neurospora* cells have two pools of proline; an intermediate or internal one, entered first by the amino acid, and also an expandable pool where it is accumulated. Zalokar thinks the site of the first pool in the cell is the water compartment of its cytoplasm, and the second is probably its endoplasmic reticulum. He considers the evidence derived from the size of these pools and the rate of incorporation indicates that the time needed to make a protein molecule is a few seconds or less.

This work is reported in *Biochimica et Biophysica Acta* and is DGMS-supported.

THREE BIS(DICHLOROACETYL) DIAMINE COMPOUNDS SUPPRESS SPERM FORMATION IN MAN WITHOUT SUPPRESSING PITUITARY ACTION

Carl G. Heller, Donald J. Moore, and C. Alvin Paulsen of the Pacific Northwest Research Foundation, Inc., in Seattle, Washington working with three Sterling Winthrop bis(dichloroacetyl) diamine compounds on volunteers from the Oregon State Penitentiary reported that, unlike the steroids, these new chemicals suppress the formation of sperm without affecting the pituitary gland or the Leydig-cell functions of the testis. Moreover, unlike most nonsteroids tried before, they do not appear to be toxic. After their use (in one case for as long as 12 months), the development of sperm quickly returned to normal when the administration of the compound was stopped. The discovery of safe chemicals with specific action on the germinal epithelium should provide a new tool for the study of the process controlling the stages of sperm development in man.

The work was DGMS-supported and published in Toxicology and Applied Pharmacology.

HYPOTHALAMIC ROLE IN ANDROGEN-INDUCED FEMALE STERILITY DEFINED

Single injections of 1.25 milligrams of testosterone propionate in female rats 2 and 5 days old produced permanent sterility accompanied by adrenal and pituitary gland weight increases, ovarian and uterine weight decreases, and absence of the corpus luteum gland. Treatment at 20 days of life had no apparent effect. This was reported by Charles A. Barraclough of the School of Medicine of the University of California at Los Angeles, and the Veterans Administration Hospital, Sepulveda, California, in a paper in the journal, Endocrinology.

These findings of Barraclough agreed with previous findings in mice, and prompted questions as to how the female sterility induced by this male hormone is mediated. Further studies with Roger A. Gorski were therefore designed to shed light on this problem.

Barraclough and Gorski reasoned that the testosterone injection does not act directly on the pituitary gland since both of the female gonad-stimulating hormones from the pituitary are present in the treated animals. Presence of the follicle-stimulating hormone was evidenced by the appearance of large egg follicles in the rats. Presence of the luteinizing hormone was evidenced by the continuous estrous condition of the vaginal lining—the rats remained in heat. The authors inferred also that the injected testosterone was probably acting through the hypothalamus by interfering with the hypothalamic control signal to the pituitary for the release of enough luteinizing pituitary hormone to free the egg follicle contents at the critical time in the natural cycle of ovulation. Reasoning that the continuous state of estrus (of being in heat) would be expected to deplete the natural stores of luteinizing pituitary hormones, Barraclough and Gorski injected such hormone (progesterone) into mature testosterone-sterilized females (rats which had been treated on the fifth day of life). This hormone "repletion" alone did not produce ovulation in the rats, but it did tend to restore the natural cycle of vaginal estrous changes which had been arrested by the sterilization. When that cycle reached the point of proestrus, Barraclough and Gorski were able to prompt ovulation in these permanently sterilized animals by electrically stimulating the hypothalamus at the arcuate ventromedial complex. Further searching in the rat brain disclosed two hypothalamic sites which activate release of the pituitary gonadotropic hormones of the female.

Considering their own work with that of other workers in various disciplines, Barraclough and Gorski concluded that the preoptic area of the hypothalamus is the site on which the injured testosterone acts, and is the chief site of ovulation control, whereas the median eminence area controls a more generalized gonadotropin secretion.

The experimental evidence thus confirming their theory that the hypothalamus is responsible for androgen-induced sterility in the female was reported in a second paper in Endocrinology. The work was DGMS-supported.

COLOMINIC ACID REPORTED TO NEUTRALIZE THE ANTI-D ANTIBODY TO THE RH BLOOD FACTOR

William C. Boyd and Egli Reeves of Boston University, Boston, Massachusetts, in the course of researches on substances inhibiting the formation of Rh antibodies, have reported that colominic acid, which is formed by some strains of the common intestinal bacterium, *Escherichia coli*, can, in the low concentration of 0.006M, neutralize the dangerous anti-D but not the anti-C or anti-E antibodies found in Rh-sensitized pregnant women. Colominic acid is believed to be nonpoisonous, and is thought to be a chemical relative of N-acetyl neuraminic acid which has similar selective inhibiting effects.

Dr. Boyd is proposing to try colominic acid clinically in an effort to prevent erythroblastosis fetalis, a blood disease in the unborn children of women sensitized to the Rh blood factor.

The work was DGMS-aided and published in Nature.

CIGUATERA (RED SNAPPER) FISH TOXIN STUDIED IN HAWAII

Paul J. Scheuer, Albert H. Banner, Satoshi Sasaki, Philip Helfrich, and Charles B. Alender of the University of Hawaii in Honolulu, are investigating ciguatera toxin, a baffling poison which seriously affects people in widely scattered parts of the Pacific. The red snapper is an important article of diet or is considered a delicacy in many areas of the world, and it is important to know what makes this fish edible in some places and poisonous in others.

A first step in the identification and measurement of ciguatera toxin is the development of a consistently successful method of extraction and assay. Previous methods of aqueous extraction have proved unreliable.

A mongoose, fed raw fish containing the poison, reacts much as people do. The flesh of fish thus shown to be poisonous is then extracted with ethanol. The toxin is extracted by ether from aqueous ethanol. The final purified product when tested on mice in dilute amounts to (0.2 mgm/gm) produces death. Ether extracts of a nonpoisonous specimen have to be given in 1.5 mgm/gm doses to kill a mouse.

With a practical test for toxicity available, it should be possible to check the fish population in a given area for safe edibility.

These findings are supported by DGMS, and reported in Nature.

PATTERNS OF DEVELOPMENTAL ABNORMALITY IN THE ORGANS OF MICE FOLLOWING ORAL VITAMIN A RESEMBLE PATTERNS KNOWN TO OCCUR NATURALLY IN MAN

Vitamin A, in large single oral doses early in the pregnancies of inbred strains of mice, consistently produced a wide variety of congenital abnormalities, some of which have never been experimentally produced but have occurred spontaneously in man. This was reported by Harold Kalter and Josef Warkany, DGMS grantees at the University of Cincinnati, Cincinnati, Ohio.

Excessive intake of vitamin A by rats has previously resulted in the production of fetal monsters o terata. The Ohio observers fed single "relatively large" doses (10,000 I.U.) of vitamin A per mouse to three inbred strains of mice at daily intervals, from the 7th to 12th days of mouse pregnancy. All three strains showed the same forms of abnormalities in the embryos on macroscopic examination 2 days before term (17½ days after conception). The seven mice treated on the 7th day showed resorption of all but 1 of 53 embryos conceived. Resorption rates declined sharply in mice treated on the succeeding days. Ninety-eight percent of the total of 198 embryos examined from the total of 92 female mice treated showed abnormalities.

Fifty-nine percent of the 179 embryos from mice treated on the 10th, 11th, and 12th days showed abnormalities, all of which fit into three known categories—cleft palate, short or missing legs, and deformations and defects of skeletal substance.

The greatest variety of abnormalities was observed in the mice of 8th day treatment. They and the 9th day mice were characterized by defects, excesses, and deformations of head, facial, and mouth tissues. Over 70 percent had cleft palate and over 30 percent had reduced or missing mouths. Defects and excesses of tissue development in jaws, tongue, and head glands were common, including many extra and displaced teeth. Reduced eye sockets combined with normally developed eyes (and consequent exophthalmost), missing eyelids, and deformed or missing ears, were also common in this group. The only other embryonic abnormalities common to the mice of 8th and 9th day treatment were those of the tail, ranging from its deformation to its complete absence.

Considered separately, the mice of 8th day treatment showed patterns of embryonic abnormality not observed in the other groups. These included cleft lower jaw; fused ribs; closed anus; exposed brain or spinal cord (exencephaly or spinal bifida); brain too large for skull ("crowded brain"); fused, malformed, and missing kidneys, ureters, and genital ducts; missing umbilical cords; displaced ovaries; and various cardiovascular abnormalities.

Ten embryos were serially sectioned for microscopic examination of internal organs. Among the experimental innovations which seemed significant in these as artificial representations of conditions occurring naturally in man, were extra teeth, tongue fused to side of mouth, thymus gland displaced from head to neck, coronary aneurysm, crossed or displaced kidneys, defects (fistulas) in rectal and bladder structures, and missing umbilical arteries.

The occurrence of about 1 missing umbilical artery in each 100 placentas has been recorded in previous studies by Little (1958), and Benirschke and Bourne (1960) in a total of 2,700 cases studied. In the total of 31 cases of missing human umbilical artery thus found, 10, or one-third, of the infants showed other congenital abnormalities as well.

Mice treated on the 8th day of pregnancy showed fewer and milder effects when treated in the spring than in the winter. A similar seasonal variation was observed over a 5-year period of treating pregnant mice with cortisone, in another study by the Cincinnati authors.

The experimental data and inferences were reported by Kalter and Warkany in The American Journal of Pathology.

EVAPORATIVE WATER LOSS OF SMALL ANIMALS MEASURED WITH INFRARED GAS ANALYZER

Using an infrared gas analyzer to measure evaporative water loss as part of water balance problems of small vertebrates in relation to their environments, a DGMS grantee has reported the versatility of the instrument as well as ratios of loss from lungs and skin in varying degrees of humidity.

The original use of crude infrared analyzers to study water loss in humans (Palmes 1948) was not satisfactory due to mechanical difficulties. Recently, however, Decker (1960) has modified the modern apparatus to study water loss in plants. Robert M. Chew, of the University of Southern California at Los Angeles, profited by knowledge of this use to turn the instrument, frequently used in carbon dioxide studies, to the study of water losses. He observed that the analyzer can be used to measure the water in air, entering, as well as leaving, an experimental chamber. He was able to measure the water loss from various animals under different degrees of atmospheric dryness and to compare the amount lost while sleeping, with that lost during exercise. Because the amount of water lost is in inverse linear relationship with absolute humidity, Chew infers that a diffusion process is involved. He recorded that desert rodents lose water much slower than white mice, and that desert reptiles lose less water than rodents. He reported that some animals lose 2 to 4 times more water when running than when sleeping. It would seem that the gas analyzer could be a very valuable tool for many physiological studies of water and carbon dioxide. The findings were published in Science.

A SERINE ACTIVATING ENZYME FROM BEEF PANCREAS

Earl W. Davie and Leslie T. Webster of Western Reserve University at Cleveland, Ohio, have investigated a serine activating enzyme from fresh beef pancreas. Chemical knowledge of how and where the amino acids (serine is one) are synthesized undergirds the understanding of physiology. Following similar methods used to explore tryptophan activating enzymes, they used hydroxamate and pyrophosphate exchange assays to discover some of the properties of this enzyme. Davie and Webster determined that the enzyme catalyzes the transfer of activated serine to soluble ribonucleic acid. When proper amounts of the new enzyme were added to serine, adenosine triphosphate, and pyrophosphatase in the presence of magnesium ions, seryl adenylate was produced identical with chemically synthesized seryl adenylate. Aging seemed to affect the activity of the enzyme, and the ratio of pyrophosphate exchange to hydroxamate formation was not uniform in all preparations, indicating a need for further purification.

These studies were DGMS-supported and were reported in the Journal of Biological Chemistry.

FOURTEENTH SYMPOSIUM IN BASIC PHYSIOLOGY

The Society of General Physiologists, with support from a DGMS grant, has held its 14th consecutive annual symposium in basic physiology to examine and critically evaluate the metabolic processes controlling and interrelating aerobic and anaerobic metabolism. The meetings were held in Woods Hole, Massachusetts, in September 1961.

Both topics and participants were chosen to cut across disciplinary boundaries in the hope that information from diverse fields would reveal unsuspected correlations and suggest new lines of scientific inquiry. This was in line also with the Society's policy of seeking to ignore the boundary between plant and animal physiology.

Upwards of 200 general physiologists attended, with specialty interests ranging from protein chemistry and biophysics to photosynthesis.

STUDIES USING ULTRAVIOLET MICROBEAM INDICATE THE IMPORTANCE OF THE NUCLEOLUS IN RIBONUCLEIC ACID SYNTHESIS

Maurice Errera and A. Hell of the Université Libre de Bruxelles, Belgium, and R. P. Perry of the Institute for Cancer Research in Philadelphia, Pennsylvania, have studied the incorporation of the radiolabeled nucleoside, cytidine, and also of various amino acids into different parts of growing HeLa cells.

Most of the cytidine is taken up into ribonucleic acid, which is known to play a key role in the process of inheritance in both plant and animal cells. From their studies the investigators postulate that the nucleolus, a round body inside the cell nucleus, plays a major role in the formation of cytoplasmic RNA.

Errera and Hell focused ultraviolet light into a microbeam small enough to irradiate areas only a few microns in diameter, and with it irradiated cell nucleoli for periods of 10 to 15 seconds. They found this amount of ultraviolet light would almost completely inhibit the normal incorporation of cytidine into the nucleolus, but would not seriously decrease incorporation into adjacent areas of the nucleus. When regions of the nucleus outside the nucleolus were irradiated, there was very little change in the incorporation pattern from that of the normal nonirradiated cell.

Comparing autoradiographs of control cells with those taken after the ultraviolet irradiation of nucleoli and subsequent incubation with labeled cytidine, the investigators found not only that ultraviolet light almost completely prevents the incorporation of any cytidine by the irradiated nucleolus, but also that cells so treated show ⅔ less incorporation into cytoplasmic ribonucleic acid than the normal cells, and ⅓ less in the rest of the nucleus.

The microbeam experiments in conjunction with measurements of nucleoside uptake indicate that ribonucleic acid is probably all synthesized in the nucleus of the cell and then migrates to the cytoplasm, and that, within the nucleus, the nucleolus is the most important area involved in the process.

The findings were DGMS-aided and reported in *Biochimica et Biophysica Acta.*

OBSTRUCTIVE JAUNDICE IN RABBITS FOUND TO DECREASE LIVER MICROSOMAL METABOLISM OF DRUGS IN ROUGH PROPORTION TO THE AMOUNT OF LIVER CELL DAMAGE

Textbooks state that damaged liver function may result in greater drug action. In certain cases such changes in the action of a drug may be related to bodily changes in drug metabolism. Many drugs are metabolized by enzymes in liver microsomes. Biochemical and cytological studies have shown that certain bile acids can destroy microsomal structures.

James R. Fouts and Edwin F. McLuen, of the State University of Iowa at Iowa City, Iowa, reasoned that obstructive jaundice might increase reaction to a given dose of a drug because of the destructive effects of bile acids on the liver cell microsomes and the drug-metabolizing enzyme systems in these intracellular particles.

They studied the microsomal metabolism of chlorpromazine, hexobarbital, 1-amphetamine, codeine, acetanilid, and aminopyrine in livers from normal rabbits versus rabbits with varying degrees of surgically induced obstructive jaundice. These metabolisms were studied by incubating liver fractions with the various drugs. Liver damage was estimated histologically.

These drug metabolisms were markedly depressed in jaundiced animals with severe liver damage. In livers where damage was only moderate, the metabolism of hexobarbital was near normal while the other drugs were metabolized more slowly than normal. The actions of hexobarbital were assessed *in vivo* as well. In rabbits with severe liver damage caused by the jaundice, a dose of hexobarbital easily tolerated in normal rabbits was often fatal. Moderate liver damage had little effect on duration or intensity of hexobarbital action—a finding consistent with the *in vitro* results.

The effects of deoxycholate added *in vitro* to normal liver fractions were studied. The close similarity between curves showing the loss of enzyme activity and the dissolution of microsomes as functions of deoxycholate concentration, and the fact that the enzyme inhibition both *in vivo* and *in vitro* is apparently irreversible suggests a mechanism of "inhibition by destruction." The concentrations of deoxycholate used *in vitro* were those believed to be possible in livers from jaundiced animals.

This work was supported by DGMS and published in the Journal of Pharmacology and Experimental Therapeutics.

HEROIN EFFECTS MEDIATED BY MAM AND MORPHINE

Although the narcotic and addictive effects of heroin are greater than those of morphine, past pharmacologic studies have tended to indicate that administered heroin is quickly and virtually completely transformed to morphine. The idea that heroin might act instead through conversion to 6-monacetylmorphine (MAM) was suggested by two groups in 1935, but experimental evidence published in 1942 seemed to refute this idea.

E. Leong Way and coworkers have concluded from studies in mice that the effects of heroin are mediated by MAM as well as morphine. They found that heroin penetrates the central nervous system largely as MAM; only slightly as morphine. They found the direct role of heroin itself transitory and negligible because of its rapid disappearance from the tissues (half-life of 2.5 minutes). The disappearance is accompanied by the appearance of MAM, followed later by that of morphine. The peak effects of heroin are attributable to the actions of both MAM and morphine. The persistent effects are attributable mainly to morphine, which endures longest in the tissues. The investigators believe past studies missed the importance of MAM as a metabolite, because it tends to deteriorate during extraction procedures unless special precautions are taken.

Portions of the work by Way's group have been presented on various occasions since 1957. The completed work appeared in the Journal of Pharmacology and Experimental Therapeutics. John W. Kemp, Joseph M. Young, and David R. Grasetti coauthored the latter publication, reported from the University of California, in San Francisco, and the University of Berne, Switzerland. DGMS research grants partially supported the studies.

Research in General Medicine

FOLIC ACID IN PHYSIOLOGIC (MAINTENANCE) DOSAGE FOUND USEFUL IN DIFFERENTIAL DIAGNOSIS OF MEGALOBLASTIC ANEMIAS

Small amounts of folic acid will correct megaloblastic anemia when it is a consequence of folic acid deficiency but not when the anemia is due to B_{12} deficiency, according to Richard A. Marshall and James H. Jandl of Harvard University in Boston, Massachusetts. Confirming previous work, the authors indicate that less than 0.5 mg a day will supply the normal adult requirement of folic acid. They find that daily intramuscular injections of 0.4 folic acid produces as rapid and as great improvement in patients with folic acid deficiency as the customary large (10–20 mg) dosage.

The few patients, who do not respond to small doses but do to large, and who at the same time are not B_{12} deficient according to laboratory tests, are thought to have a defective utilization of folic acid rather than a simple deficiency.

Since the B_{12} deficiency anemias do not respond to the small doses but do (at least temporarily) to the large, Marshall and Jandl believe the use of the small physiologic (maintenance) dose affords a useful diagnostic tool, simpler and more conclusive than measuring serum levels of cyanocobalamin and folic-acid-like activity.

Their studies were reported in the A.M.A. Archives of Internal Medicine. DGMS grants supported the work.

The basic and clinical findings confirm and extend those reported earlier by Herbert (Blood, February 1960), which were also aided by DGMS research grants.

PROGRESS AND PROBLEMS IN THE FIELD OF SHOCK

A conference on shock, the first of its type held in 10 years, was initiated and sponsored by two committees of the National Academy of Sciences-National Research Council to evaluate recent knowledge and to stimulate wider interest. DGMS financed the publication of the conference proceedings in Federation Proceedings. The subjects covered were: experimental shock models, circulatory changes, metabolic aspects, permetability factors and radiation injury, bacterial factors, and vascular surgery in shock. There were also round-table conferences which further touched on hemostatic mechanisms in shock, and anesthesia in shock. The work is of continuing importance in general medicine and may assume greater importance in the future.

A STUDY OF THE ORGANIZATION AND FUNCTION OF HOSPITAL-BASED HOME CARE PROGRAMS

On the premise "that organized care of patients in the home is a desirable resource in the total complex of health services * * *" David Littauer, I. Jerome Flance, and Albert F. Wessen of the Jewish Hospital, St. Louis, Missouri, have reported a detailed study of the organization and operation of a home care program in the Jewish Hospital.

Administration of this program is closely linked to patient service by weekly conferences. The administrative staff consists of a medical director, the chief of the department of social work, and the head of the local visiting nurse association. Administrative responsibilities include record keeping, the establishment of standards, admissions, assignments to physicians, and final discharge or other placement of home care patients. The service staff is comprised of the teams actually working with the patients and includes physicians, surgeons, dentists, social workers, nurses, nutritionists, physical and occupational therapists, laboratory technicians, and housekeepers. Residents from the house staff are also used in selected instances. The hospital guarantees patient hospitalization as needed, maintaining 1 hospital bed for each 10 home care patients for this purpose.

In surveying 14 other home care programs scattered over the country, Littauer, Flance, and Wessen found that many more patients were referred than later proved acceptable, and conclude from this that careful screening of referrals is essential. They state that patient candidates must not be too sick, must have illnesses requiring physician supervision, not just continuous nursing, and must have a suitable home close enough for hospital personnel to reach, to profit from home care. The investigators found that most of the home care patients studied were economically depressed; that the sex ratio of such patients is 3 women to 2 men; that most applicants for home care are over 45 (although home care is adaptable for all ages); and that new admissions each year average about 2½ times the daily case load. The types of diseases treated varied with the interests of the staff, but long-term cerebrovascular, heart, cancer, neurological, tubercular, and surgical recovery problems were all found suitable for home care. Approximately one-half of all home care patients will be eventually discharged to outpatient status or as recovered, about one-fifth will die, one-seventh will be rehospitalized, and the rest transferred to nursing homes or other types of care.

The report indicates that the selected home care patient does at least as well in the home as in the hospital, and may even live longer or recover more readily than in the hospital; that his treatment cost per day is less ($3–$5 at home vs. $25–$45 in the hospital); and that home care programs free hospital beds needed for acutely ill patients. Moreover, these programs provide valuable training for young doctors, nurses, and social workers in adapting professional skills to home environments. Also a system of home care increases community acceptance of hospitals as health centers. One unexpected dividend of the system is the increased number of individuals who come to think of a hospital as a place interested in sick people rather than as an institution impersonally concerned only with disease.

The present obstacles to the growth of home care programs are discussed and some solutions offered. The growing need for such plans and possible areas of study and research are suggested, and differences between hospital-based and community-based systems are discussed.

This work, Home Care, published as Number 9 in the Hospital Monograph Series of the American Hospital Association of Chicago, Illinois, is supported by a DGMS grant.

WAKEFULNESS AS A CEREBRAL STIMULANT TO BREATHING

There is a widespread assumption that in resting man and animals the rate and volume of respiration depends upon the carbon dioxide tension in the blood. If a person overbreathes and so loses enough carbon dioxide via the lungs to lower its level in the blood, the stimulus to the breathing center ceases and the person stops breathing until enough carbon dioxide accumulates in the blood to re-stimulate the breathing process. This temporary stoppage, or apnea, associated with low carbon dioxide tension, is found regularly in overventilated anesthetized people, but few cases have been reported from conscious people. The few experiments recorded yield data that are inconsistent. The ones reporting apnea were done by people experimenting on themselves and expecting to find apnea.

B. Raymond Fink of Columbia University and the Presbyterian Hospital in New York City, tested 13 healthy anesthesiologists, all familiar with his equipment but unacquainted with the purpose of the experiment. He used both mechanical and voluntary forced breathing methods, sometimes reducing the carbon dioxide tension level below 15 mm. Hg (the normal level is about 40 mm. Hg). In only one case was there any appreciable change in the breathing rate, and that occurred as apnea when one tired subject dozed off for a moment. The breathing instantly started when he woke as his name was called.

These observations are interpreted to mean that cerebral activity associated with wakefulness or consciousness probably plays a more important role than the blood level of carbon dioxide in maintaining rhythmic breathing. When cerebral activity stops, either naturally as in sleep or with the intervention of drugs, the breathing stops more readily when the carbon dioxide tension falls. Conversely, the cerebral activity change from unconsciousness to wakefulness, as at birth and during recovery from anesthesia, produces a strong stimulus to breathing.

These DGMS-supported findings have been published in The British Journal of Anaesthesia, Anesthesiology, and the Journal of Applied Physiology.

FIVE-YEAR STUDY OF MULTIPLE-SCREENING CLINIC RESULTS IN NEGATIVE EVALUATION

Evaluating the effects of public health programs is difficult and this study found no evidence that a multiple-screening clinic in Baltimore, Maryland, had benefited those who attended. In a multiple-screening program a sample of a given population is asked to take laboratory tests designed to separate those who may have various undetected ailments from those who have not, and to induce the former to seek treatment early. Because the procedures are quick, free, and involve no initial personal contact with a physician, public health workers thought they might appeal to a different group of people than periodic medical examinations do.

In the present DGMS-aided study, Charles M. Wylie, of Johns Hopkins University in Baltimore, Maryland, reported in Public Health Reports that his studies indicate the multiple-screening clinic begun in 1954 in Baltimore and followed up 5 years later by a questionnaire and by telephone, appealed more to whites between 25 and 54 years of age than to any other group. The participants had more stable residential habits, a higher economic status, were more cooperative about returning questionnaires, and probably visited physicians and entered hospitals more frequently than the nonparticipants. However, the mortality rate was the same for both groups, though the causes of death were different.

PREPARATION OF A SET OF STANDARD DEATH RATES FOR PREMATURE INFANTS TO ENABLE COMPARISON OF HOSPITAL RECORDS

Despite a considerable amount of work designed to help premature infants survive, there has been wide variation in reported hospital mortality rates among these subjects. It has been difficult to evaluate the causes of the diversity of hospital fatality rates. Moreover, when infants are transferred to special premature centers, the mortality experience is usually distorted because of the marked influence of the factor of age-on-admission. As a result it has been very difficult to compare and evaluate the various procedures designed to help these children.

William A. Silverman of Columbia University, New York City, has compiled a set of standard death rates based on a 3-year study of nine premature centers in New York City. These should serve for years as reference tables for hospitals to use to adjust their original data for comparison purposes.

This compilation was DGMS-supported and the tables have been published in Dunham's Premature Infants.

NEW METHOD USING BASOPHIL BLOOD CELLS PERMITS TESTS FOR ANAPHYLAXIS AND FURTHERS LIPEMIA STUDIES

DGMS and the Department of the Army have supported Dr. Walter B. Shelley of the University of Pennsylvania in Philadelphia, and Dr. Lennart Juhlin, presently at the University Hospital in Uppsala, Sweden, in their investigations on histamine and heparin-related reactions in the body. The mast cell in connective tissue has been widely studied, but its cousin in the blood, the basophilic granulocyte, is so fragile and so rare (the authors estimate approximately one to each 300,000 red blood cells) that research into its physiological relationships has not been possible. After 2 years of work, Shelley and Juhlin have devised a way of concentrating these cells and studying them.

Basophils are apparently repositories of both histamine and heparin, and, as such, are of interest in the physiology of allergies, particularly the very serious, often fatal, cases of anaphylaxis due to cold and to penicillin. They are also of concern in the process of fat transport and its relation to atherosclerosis.

In a series of three papers, these investigators reported their findings: (1) that the degranulation of the basophil with release of histamine into the blood, as well as the degranulation of the mast cell, is cytologically demonstrable in the case of hives caused by cold (Journal of the American Medical Association); (2) that the degranulation of the basophil can be used in vitro as a test for patient anaphylactic sensitivity to cold, to penicillin, and to other drugs (Nature); (3) that the clouding of blood (due to fat particles) after eating is closely associated with degranulation of the basophil. The authors consider this degranulation to be associated with the fat clearing reaction as a mechanism for releasing heparin into the blood, and stimulating an increase in lipoprotein lipase (American Journal of the Medical Sciences).

RESISTANCE TO MOST INSECTICIDES FOUND IN MANY YELLOW FEVER MOSQUITOES IN PUERTO RICO AND THE VIRGIN ISLANDS

Irving Fox and Ileana Garcia-Moll of the University of Puerto Rico Medical School in San Juan, have maintained a colony of the Isla Verde strain of the *Aedes aegypti* mosquito since 1959. These insects are resistant to both DDT and dieldrin, the commonly used insecticides with which public health authorities usually control the mosquito population and hence the incidence of yellow fever in the tropics. When wild mosquitoes from various parts of the northern coast of Puerto Rico and from St. Croix in the Virgin Islands were tested, a similar widespread resistance was found. This represents a potential public health hazard of great importance.

The investigators claim their highly resistant colony of insects is becoming more resistant with time, and is especially useful for testing old and new insecticides. They note that resistance to organic phosphates is also increasing. Apparently resistance to Bayer 29493, which the investigators found the most effective insecticide against adult mosquitoes, has not yet developed.

These studies were reported in Science.

DIVISION OF BIOLOGICS STANDARDS—HIGHLIGHTS OF PROGRESS IN 1961

The accelerated pace of research in the area of infectious diseases has resulted in a significant increase in the number, complexity, and diversity of biological products. At the close of the calendar year, 284 such products were licensed under the provisions of the Public Health Service Act for commercial use in this country and abroad.

These products, which include the vaccines, antitoxins, therapeutic serums, and human blood and its derivatives, are developed for the most part from pathogenic or potentially pathogenic micro-organisms. Their preparation requires careful control in order to minimize safety hazards which might occur in the course of processing, and to insure final products of satisfactory potency. Accuracy is essential in every step, for the end product is the preservation of human life.

Responsibility for the administration of these control measures resides with the Division of Biologics Standards. Effective administration of these responsibilities requires the design and development, within a research context, of adequate and practical standards for the production and testing of biologics, careful surveillance of production methods, and the continuous improvement of testing procedures. Thus the control program of the Division of Biologics Standards is necessarily supported by an active and flexible research program, enabling the Division to keep pace with the rapid development of new and improved immunizing agents and to prepare physical references as well as to develop testing procedures for these products once they are ready for commercial production.

The research programs of the Division's six laboratories—Bacterial Products, Biophysics and Biochemistry, Blood and Blood Products, Control Activities, Viral Immunology, Virology and Rickettsiology—include a diversity of projects, many of immediate practical urgency, and all having direct relation to the prime responsibility of the Division.

RESEARCH AND PROGRAM DEVELOPMENTS

HEPATITIS PATIENTS SHOW ANTIBODY TO A NEWLY ISOLATED VIRUS

The presence of antibody in hepatitis patients against a newly isolated virus was reported last week at the Federation of American Societies for Experimental Biology meeting by Dr. J. P. O'Malley, Division of Biologics Standards, Laboratory of Virology and Rickettsiology.

The virus, referred to as the A–1 agent, was recovered by Dr. O'Malley from rabbit kidney tissue cultures inoculated with material from the NIH icterogenic human plasma pool. The pool, established in 1951, is known to have induced homologous serum jaundice in human subjects, although attempts to recover a viral agent from laboratory hosts inoculated with this material have not been successful. The A–1 agent has been recovered only on one occasion, despite numerous attempts by Dr. O'Malley to reisolate it. Moreover, it has not been recovered from other known icterogenic materials.

The A–1 agent propagates readily in a number of primary and continuous cultures, including monkey, rabbit, chick, and human cells. Moreover, it produces cytopathic effects in all of these cultures except in primary monkey kidney cells. To date, however, it has failed to cause disease or gross lesions in mice, guinea pigs, rabbits, embryonated eggs, rhesus monkeys, suckling hamsters, and mice inoculated by various routes.

Tests for viral antibodies against the A–1 agent in stored sera taken some years ago from human volunteers infected with material from the NIH icterogenic pool indicate that such antibodies were not present prior to inoculation, but were regularly found during convalescence. These findings were obtained not only with volunteers infected with the most extensively studied icterogenic pool, but also in those who developed jaundice following inoculation with five other icterogenic materials.

Stored sera from a group of volunteers presumed to have been infected with infectious hepatitis rather than with serum hepatitis virus had antibodies against the A–1 agent. However, reexamination of the clinical records revealed a disease with a long incubation period, raising a question as to whether this group might not originally have had serum rather than infectious hepatitis.

In a series of cases of infectious hepatitis contracted in the Far East and in the United States by military personnel, there was no demonstrable rise in A–1 antibodies, although in a few instances A–1 antibodies were present at the same level in the early and late sera. On the other hand, in one outbreak of disease diagnosed as infectious hepatitis which occurred in the Mediterranean area, two-thirds of the convalescent sera tested contained A–1 antibodies; early sera has not yet been tested.

The current work by Dr. O'Malley with the A–1 agent is still in a preliminary phase. It is one of many efforts by investigators throughout the world to transmit the agent of homologous serum jaundice in tissue culture systems and laboratory animals as the first step toward eliminating the contamination of blood products with this form of viral hepatitis.

MONGOLISM ASSOCIATED WITH RAT VIRUS INFECTION IN HAMSTERS

Rat virus, a widely spread latent infection of normal rats, has been found to induce a disease in suckling hamsters that resembles mongolism. Dr. Lawrence Kilham, Division of Biologics Standards, Laboratory of Virology and Rickettsiology, has reported this finding in Virology.

The original isolation of rat virus from rats bearing spontaneous or transplantable tumors, its multiplication in rat embryo tissue cultures, and its ability to agglutinate guinea pig erythrocytes, were reported by Dr. Kilham several years ago. More recently he has found that rat virus is infectious for suckling hamsters, with acute illness and death usually following an intracerebral inoculation of the agent rat virus.

A second and more chronic disease develops when a minimal dose of rat virus is administered, or when the suckling hamsters are close to the age limit of susceptibility. This disease consists of stunted growth, broadening of the facial bones, protruberance of the eyes, occasional eye infection, poorly formed or missing incisor teeth, swelling of the tongue and lower gums, feebleness, and unusually gentle behavior.

In one experiment, six litters of 4-day-old hamsters were inoculated with rat virus tissue culture fluid at a dilution of 10^{-1}. Twelve of the 47 sucklings involved survived the acute phase of the disease and became mongoloid dwarfs.

Two other viruses are known to induce dwarfism in animals. An agent isolated from transplantable human tumors, described by Dr. H. W. Toolan, et al., Sloan Kettering Institute for Cancer Research, leads to a type of mongolism in hamsters which closely resembles that caused by rat virus. NIH Drs. Sarah Stewart, Bernice Eddy, and M. F. Stanton have found that the SE polyoma virus can lead to a stunting of growth in mice.

The rat virus appears to be a close relative of the polyoma agent, as indicated by the type of intranuclear inclusion bodies produced and by various properties relating to stability and hemagglutination.

HOST RANGE OF SE POLYOMA VIRUS EXTENDED TO GUINEA PIG

It has been shown in earlier studies that the production of tumors by the SE polyoma virus (discovered in 1957 by Drs. Sarah E. Stewart, National Cancer Institute, and Bernice E. Eddy, Division of Biologics Standards) was not restricted to its original host, the mouse. Other animal species—the hamster, rat, and rabbit—have also been found to develop various forms of neoplasms when infected with the virus.

More recent investigation now extends the host range to the guinea pig. Drs. Bernice Eddy, Gerald Borman, Ruth Kirschstein, and Mr. Robert Touchette, Division of Biologics Standards, have found that the guinea pig, when infected with SE polyoma virus, also develops neoplasms.

The tumor-inducing effect of the SE polyoma virus varies in the different species of animals which have been tested. Neoplasms were found to develop more slowly in the guinea pig than in the hamster, mouse, rat, and rabbit. Gross tumors occurred at the site of inoculation, but histologic examination showed tumors in the liver, lung, spleen, adrenal, and kidney of some of the guinea pigs. In the other animal species studied, neoplasms may occur at the site of inoculation, although they are usually found in selected tissues. Lesion most frequently occurs in the parotid glands of mice; in the heart, kidneys, liver, or subcutaneous tissues of hamsters; in the kidneys or subcutaneous tissues of rats; and in the subcutaneous tissues of rabbits.

Gross tumors, considered to be sarcomas, were evident in 28 of the 47 guinea pigs examined when the virus was given either subcutaneously or intramuscularly, but proportionally more tumors developed when the animals were infected by the intramuscular route.

The virus isolated from tumor tissue of one guinea pig was found to be identical in all respects with the SE polyoma virus used to infect the guinea pigs.

NEOPLASMS INDUCED IN HAMSTERS BY INJECTION OF EXTRACTS FROM PRIMARY MONKEY KIDNEY CELL CULTURES

Experiments by DBS investigators with rhesus monkey kidney cell cultures show that injection of newborn hamsters with extracts of certain lots of cell cultures are followed several months later by occurrence of neoplasms at site of injection.

The induction of neoplasms in newborn hamsters by the injection of primary rhesus monkey kidney cell culture material has been reported by Dr. Bernice Eddy and associates, Division of Biologics Standards, in the June issue of the Proceedings of the Society for Experimental Biology and Medicine.

Extracts of certain lots of rhesus monkey kidney cell cultures were inoculated into 154 newborn hamsters. Of these, 109 developed neoplasms between 99 days and 9 months after the injection of cell extract.

Transplants were made from three of the induced tumors to newborn hamsters which in turn developed tumors in 13 to 48 days. Tumor tissue from one of the three original neoplasms tested for transplantability were passed from hamster to hamster in series five times; neoplasms developed in all of the surviving animals within 6 to 24 days.

The hamster tumors were not transmissible in the usual virological sense, however, since extracts of the tumor tissue failed to induce tumors. Nor were any changes indicative of a virus observed when extracts of a tumor or tumor mince were inoculated with primary mouse embryo, primary vervet monkey kidney cells, or a continuous line of rhesus monkey kidney cell cultures.

Dr. Eddy and her co-workers found that, while there were general similarities in the tumors produced in hamsters by the rhesus monkey kidney cell cultures and those induced by SE polyoma virus, they differed somewhat in their distribution and cellular detail. The neoplasms appeared to be undifferentiated sarcomas in subcutaneous tissue, kidneys, and lungs.

RELATION OF THE ANTIVIRAL ACTION OF INTERFERON TO EMBRYONIC DEVELOPMENT

Investigations, reported in Lancet by Dr. Alick Isaacs, National Institute for Medical Research, London, and Dr. Samuel Baron, National Institutes of Health Laboratory of Viral Immunology, Division of Biologics Standards, indicate that interferon may be formed in the body as a protective response to virus infection.

Interferon, a substance produced by living cells under the stimulus of viral infection, was so named by its discoverer, Dr. Alick Isaacs, because it interferes with the propagation of viruses. It has been shown to protect the cells in vitro against a wide range of virus infections.

The hypothesis is that interferon acts by causing an uncoupling action on oxidative phosphorylation, thus limiting the amount of adenosine triphosphate (ATP) available for viral synthesis. The decreased antiviral action of interferon in cancer cells would seem to correlate with Warburg's evidence (1956) that cancer cells can form by anaerobic processes all the ATP they require for growth.

Since embryonic cells also show a high rate of anaerobic glycolysis, Drs. Isaacs and Baron, reporting in Lancet, have postulated that the cells should also show a similar resistance to the antiviral action of interferon during an early stage of their development and, later, assume the behavior characteristics of cells from adult tissues. To investigate this possibility, they tested the antiviral action of interferon on the growth of influenza virus in chick and mouse embryo tissue at different stages of embryonic development. The 11-day-old tissues produced twice as much virus but 20 times as much interferon as the 6-day-old cells.

The authors suggest that if this is true of the young human embryo, it might explain why maternal infection with rubella virus during the first 3 months of pregnancy often leads to congenital malformations, whereas infection after the third month rarely does. Their assumption is that if the embryo is infected during the first trimester, it produces very little interferon. At a later stage of development, interferon is produced and the viral infection is more effectively limited.

The authors further speculate that the antiviral action of interferon has developed in the course of evolution as an adaptive response to superficial virus infection. The original functions may have been to control cellular division by controlling the supply of ATP. The cancer cell, would, then, be one that has escaped from the control of interferon.

ROLE OF ANTIBODY IN RECOVERY FROM VACCINIA VIRUS INFECTION

In recent Division of Biologics Standards studies on the role of antibody in recovery from infection with vaccinia virus, irradiated animals, in which no detectable neutralizing antibody could be demonstrated, recovered from vaccinia infection as rapidly as did nonirradiated animals. The results suggest that production of neutralizing antibody was not necessary for recovery. These studies were recently reported in the Journal of Immunology.

In studies conducted by Drs. Robert M. Friedman and Samuel Baron, Laboratory of Viral Immunology, Division of Biologics Standards, vaccinia virus was used to infect Hartley strain guinea pigs. The factors of virus growth, local antibody, circulating antibody, gross pathology, histopathology, and skin sensitivity were examined during the infection and recovery periods.

Previous studies had shown that 300-roentgen X-radiation to guinea pigs inhibited the antibody response but not the development of delayed sensitivity to nonliving antigens. With this in mind, the investigators subjected the guinea pigs to 300-roentgen X-radiation 24 hours before infection with vaccinia virus. The sequence of events following infection was essentially the same as in nonirradiated animals with the major exception that antibody was not detected in serum as late as 28 days after infection, nor was it detected in the lesion at the time of elimination of virus.

In contrast to the inability to produce antibody, the animals were found to develop delayed skin reactions to vaccinia antigen on the fourth day. These results indicate that guinea pigs recover from vaccinia infection in the absence of antibody production, but in the presence of delayed hypersensitivity. The present results do not permit final evaluation of the role of delayed sensitivity in recovery from virus infection.

Neither delayed hypersensitivity nor interferon were excluded as factors in recovery, and their relative importance remains undetermined.

SAFETY TEST FOR POLIOMYELITIS VACCINE ENHANCED

Division of Biologics Standards studies have demonstrated that intraspinal inoculation of monkeys with concentrated inactivity poliomyelitis vaccine is more sensitive to poliovirus than the original monkey safety test. It was also demonstrated to be more sensitive than cell cultures to residual poliovirus in some vaccine lots which infected man. These studies, conducted by Drs. Gerald L. Van Hoosier, Jr., and Ruth L. Kirschstein, and coworkers, of the Division's Laboratory of Viral Immunology, were recently reported in the American Journal of Hygiene.

Previous studies by the investigators had shown the intraspinal inoculation rout to be the most sensitive in detecting minimal amounts of live virus in formaldehyde-treated vaccine. In this study, this route was used to determine the effect of larger volumes of the poliovirus vaccine in the monkey safety test.

Previously, 50 milliliters of each vaccine were injected into 20 monkeys for the monkey safety test, and 4,500 milliliters were used for the tissue-culture test. In order to use increased amounts of poliomyelitis vaccine for intraspinal inoculation as part of the monkey safety test, a method of vaccine concentration (ultracentrifugation with added gelatin) was used. This procedure indicated a considerable enhancement of the sensitivity of the monkey safety test.

The findings indicated the advantage of the use of concentrated vaccine in the monkey test over current procedures for detecting, at a low level, certain types of live virus which may persist after formalin treatment. The findings also provided a sensitive in vivo method comparable to the culture tissue safety test for detecting live virus in large-volume samples of poliomyelitis vaccine.

These stuides indicate the possibility of increasing the margin of safety of the monkey test. It should be noted, however, the present methods have been satisfactory as judged by the favorable results obtained since 1955.

SV-40 RESISTANCE TO INACTIVATION BY FORMALDEHYDE REPORTED

The discvoery of the presence of an extraneous virus in Salk poliomyelitis vaccine and adenovirus vaccine is reported by Dr. Paul Gerber, Dr. George A. Hottle, and Mr. Robert E. Grubbs, of the Division of Biologics Standards Laboratory of Viral Immunology, in the November issue of the "Proceedings of the Society for Experimental Biology and Medicine."

This virus, identified in 1960 by Sweet and Hilleman, multiplies readily in the kidney cell cultures of the rhesus and cynomolgus monkey but, unlike other known simian viruses, causes no cellular damage. However, in African green monkey (grivet, cercopithecus, vervet) kindey cell cultures, distinctive changes in the cytoplasm occur as the virus grows. Because of these changes which eventually destroy the cells, the virus is called the vacuolating virus, and has been classified by Hull as SV–40.

In their report, Sweet and Hilleman presented data which indicated that formaldehyde used in the manufacture of Salk vaccine would inactivate SV–40, as well as the poliovirus itself. Results obtained in the Division of Biologics Standards study showed that the course of treatment of SV–40 with formaldehyde was characterized by a biphasic reaction. In the first phase, the major portion of the viral population was inactivated at approximately the same rate as the poliovirus. The second phase indicated persistence of a residual fraction which resisted inactivation by formaldehyde. The reason for this is not known. Further studies are necessary to determine if there is variation in the viral population with regard to susceptibility to formaldehyde or if reactivation of "inactivated" particles occurs. Of further interest was the remarkable thermostability that SV–40 exhibited. The virus was found to retain its full degree of infectivity after heating at 37° C. for 14 days.

With this evidence of resistance of SV–40 to inactivation by formaldehyde, the Division of Biologists Standards group examined random samples of commercial lots of Salk vaccine for the presence of the virus. In four out of eight samples a virus identified as SV–40 was found to be present. In similar studies of the adenovirus vaccine, also prepared from monkey kidney tissue cell cultures, all three samples tested were found to contain SV–40.

These studies revealed that, due to the marked delay in the appearance of cell damage caused by SV–40 when present in the formaldehyde-treated vaccine, it was necessary to lengthen the observation period from 10 to 28 days in order to assure the maximum sensitivity for detection of the virus.

The occurrence of virus in some lots of vaccine may be due to several factors; e.g., the species of monkey from which cell cultures are derived for virus production, the quantity of SV–40 virus present in the seed strains, or variations in manufacturing processes.

Since the Public Health Service regulations for the commercial production of viral vaccines require that no adventitious agents be present in these vaccines, no Salk vaccine or adenovirus vaccine can be released until tests in African green monkey kindney cell cultures are made.

MASSIVE PLATELET-RICH PLASMA TRANSFERRAL USES SINGLE DONOR

A safe procedure for separating platelets from red blood cells and plasma, using simple plastic equipment, has been developed by Dr. Allan Kliman, Division of Biologics Standards, and Drs. Emil J. Freireich, Lawrence Gaydos, and Leslie Schroeder, of the National Cancer Institute. The work was reported by Dr. Kliman at the eastern section meeting of the American Federation for Clinical Research, early this year.

The procedure consists of taking whole blood from a donor, immediately separating out the plasma and platelets for transferal to the patient, and returning the red cells to the donor. The return of the red cells makes it possible to withdraw amounts of plasma as large as 1,000 milliliters per week for periods up to 6 weeks from the same donor with no harmful depletion of protein or blood cells. Since only one donor is involved, the risk of hepatitis is lessened.

Although repeated doses of platelets from the same donor were administered to each of six leukemic children, the platelet response remained satisfactory and the treatment was repeatedly effective in controlling hemorrhage.

The data obtained indicated that the donor platelets did not provoke specific immunity in the patient studies, and suggests that platelet plasmapheresis may be a practical means of providing therapeutic quantities of hemostatic plasma for thrombocytopenic patients.

STUDY OF SIMIAN VIRUSES INCLUDES CAPTURE OF MONKEYS

The Division of Biologics Standards has expanded its investigation of viruses indigenous to monkeys and monkey kidney tissue cultures, in relation to the epidemiology of virus diseases of monkeys and to the preparation and control of various virus vaccines. Dr. Gerald L. Van Hoosier, Division of Biologics Standards Laboratory of Viral Immunology, is in charge of the program.

Conditions of trapping, as well as handling and shipping, are important factors in obtaining healthy monkeys for use in the poliomyelitis and measles vaccines control program at the Division of Biologics Standards.

In order to study these conditions at close range, Dr. Van Hoosier and Dr. Harry M. Meyer, Jr., Laboratory of Virology and Rickettsiology, went to the Philippines this spring to obtain blood samples from cynomologous monkeys, which are being considered for possible use in the vaccine control program, and to India to supervise the trapping and handling of 115 rhesus monkeys from the moment of capture in the jungle to their arrival at the National Institutes of Health. Dr. Van Hoosier is primarily concerned in the biology and epidemiology of simian viruses in general; Dr. Meyer is investigating two specific viruses and their relation to the monkey—the measles virus and the vacuolating virus.

Dr. Van Hoosier's unit will study the monkey serum specimens in an effort to elucidate the epidemiology of simian viruses in the natural host. These data should provide information as to the source of infection with these agents, as well as to suggest methods of handling to prevent the spread of such infection. Such information is essential to ensuring a supply of healthy monkeys for the production and testing of viral vaccines. His work is also directed toward building up a collection of prototype viruses, type specific antisera, and detailed data on the viruses which are encountered in work with monkey tissue.

STUDY OF MONKEY B-VIRUS INFECTION USED IN TEST PROCEDURES

Recognition of characteristic lesions of Virus-B infections in the central nervous system of monkeys used in testing procedures makes it possible for virologists to be warned of the dangers of handling such infected tissues.

Virus-B is one of the 40-odd simian viruses that have been encountered in monkeys and monkey kidney tissue cultures. Little is known of the pathogenicity of these animal viruses, except Virus-B which, although it generally causes only a mild illness in monkeys, is capable of producing fatal encephalitis in human beings. Sixteen such infections, 14 of them fatal, have occurred since 1937 in laboratories in England, Canada, and the United States among laboratory personnel engaged in research involving monkeys and monkey tissue material. It is therefore essential that extreme caution be exercised when handling this potentially infected material.

In the Division of Biologics Standards laboratories, virus isolation procedures are required on the central nervous system (CNS) tissue of all monkeys showing histologic lesions, that are used for safety testing of virus vaccines.

In a study reported in the American Journal of Pathology, Drs. Ruth L. Kirschstein, Gerald L. Van Hoosier, and C. P. Li have described the lesions found in cortisone-treated monkeys after intraspinal, intrathalamic, and intramuscular inoculation of inactivated poliomyelitis vaccine. In contrast to the lesions in naturally occurring Virus-B infection in monkeys, these lesions are severe and extensive throughout the CNS and bear a marked similarity to those found in fatal human cases of B-virus infection. The DBS investigators believe that the lesions are related to reactivation of latent Virus-B by the intraspinal inoculation and of vaccine and the use of cortisone. The presence of neutralizing antibodies to Virus-B in the serums of two of the monkeys under study by the investigators before inoculation of the vaccine supports this belief, and confirms the findings of Sabin and others that apparently healthy monkeys may have variable levels of neutralizing antibodies to Virus-B. Moreover, isolation of this virus from normal kidney cell cultures has occurred on several occasions, indicating that this virus can remain latent in monkey tissues for long periods of time.

The recognition by pathologists of these lesions as Virus-B infection will make it possible to warn virologists of the danger so that every precaution can be used in handling the infected tissues during attempts at virus isolation.

TYPE I LIVE ORAL POLIO VACCINE LICENSED FOR COMMERCIAL USE

On August 16, the pharmaceutical firm of Pfizer, Ltd., Sandwich, England, was licensed to manufacture type I poliomyelitis vaccine, live, oral, for commercial use in the United States. Upon completion of final tests by the Divition of Biologics Standards to determine that each of five lots submitted in support of application for license met prescribed standards, the license was signed by DHEW Secretary Ribicoff at the recommendation of Surgeon General Terry. This procedure is in accordance with the provisions of the Public Health Service.

The vaccine, developed from the Sabin type I strain, will be marketed in the United States by Charles Pfizer, Inc., of New York. About a million doses have been purchased by the Public Health Service to be held in reserve by the Service's Communicable Disease Center for distribution at the first indication of an epidemic of type I poliomyelitis in any community in the Nation.

Funds for the purchase of a reserve supply of types I, II, and III, in the amount of $1 million, were requested by President Kennedy last spring and have been authorized by the Congress.

U.S. experience with the Salk vaccine since its introduction in 1955 has demonstrated that it is highly effective in preventing poliomyelitis. Thus far in 1961, the occurrence of the disease in the United States has been at a record low level. Preliminary figures for the first 6 months of this show an incidence rate lower than any reported for a comparable period in any previous year since 1912.

TYPE II LIVE ORAL POLIO VACCINE MEETS LICENSE REQUIREMENTS

Final tests of Sabin type II live, oral polio vaccine were completed by the Division of Biologics Standards, and a license for commercial production was granted to Pfizer, Ltd., of Sandwich, England, on October 6. Both type I and type II are marketed in this country by Chas. Pfizer & Co., Inc., of New York.

The Public Health Service's Communicable Disease Center has ordered 1,800,000 doses of the type II oral vaccine to add to its epidemic stockpile of type I. This stockpile is available to State health departments for control of impending poliomyelitis epidemics. The Service recommends that whenever a community is threatened by a type I or type II epidemic, intensive communitywide vaccination campaigns to include all persons under 50 years of age be initiated, using the appropriate type-specific vaccine.

Recently, more than 400,000 doses of type I vaccine were made available by the center for the control of an impending epidemic of the tricounty area of Onondaga, Oneida, and Madison Counties, N.Y. Type III is not expected to be available for some months; until it is licensed, the full series of Salk injections are recommended against the three types of virus causing paralytic poliomyelitis. Physicians may choose to give types I and II oral polio vaccine as a routine procedure in conjunction with the Salk vaccine injections, but large-scale immunization programs with live vaccine are not considered desirable until it is possible to initiate integrated programs with all three types.

The incidence of polio continues to remain well below that of previous years, as shown in the following table giving totals through the 38th week for the past 5 years:

	1961	1960	1959	1958	1957
Paralytic	554	1,446	3,771	1,680	1,478
Total	849	2,111	5,950	3,433	4,658

METHOD FOR SELECTIVE INACTIVATION OF VIRAL CONTAMINANTS IN VIRAL VACCINES

A method for the selective inactivation of contaminating agents in live virus vaccines was reported by Dr. C. W. Hiatt, Division of Biologics Standards Laboratory of Biophysics and Biochemstry, at the London meeting of the Seventh International Congress of Biological Standardization in August.

In his paper, "Differential Rate Methods for the Selective Inactivation of Viruses," Dr. Hiatt compared several differential rate methods, in which the adventitious virus is inactivated more rapidly than the poliovirus.

The method represents a new concept of an old technique—that of photodynamic inactivation—first reported in 1898. It involves the effect of visible light on living organisms in the presence of trace amounts of certain dyes.

Dr. Hiatt discovered that, while some animal viruses combine with the dye and thus become sensitized to ordinary light, others, including poliovirus, are highly resistant to this treatment.

To date, Dr. Hiatt has successfully inactivated 5 of the 40-odd simian viruses known to be present in monkey kidney tissues cultures. Simian viruses 1, 5, 12, 15, and 40 have been found to be susceptible to photodynamic action while SV_{16}, SV_{18}, and SV_{19} are resistant, indicating that the latter probably have some characteristics similar to the poliovirus. The Coxsackie and ECHO-1 viruses, true enteroviruses affecting the intestinal tract, are also resistant.

As described by Dr. Haitt, his method consists of the addition of a minute nontoxic quantity (1 to 10 parts per million) of the thiazine dye, toluidine blue, to the monkey kidney tissue culture fluid to be treated. The fluid is then pumped through a continuous flow apparatus, consisting of a coil of glass tubing surrounding an intensely brilliant incandescent bulb giving off visible white light. The viruses that are susceptible to photosensitization by the dye become direct targets for the destructive bombardment of light energy.

The incandescent bulb used in this process is a new type, developed by General Electric for special uses, such as the illumination of airports. Its pencil-thin, tubular shape is ideally suited to the continuous-flow method apparatus developed by Dr. Hiatt. The method could have an important application to the manufacture of live attenuated poliomyelitis vaccine, since the appearance of naturally present viruses of monkey-kidney origin at various stages in the manufacturing process of the vaccine constitutes a major production problem. The method has been successfully adapted to pilot plant operation and is feasible for processing commercial volume of the vaccine.

CHOLERALIKE EPIDEMIC STUDIED IN PHILIPPINES

At the request of the Secretary of Health of the Philippines, Dr. John C. Feeley, of the Division of Biologics Standards Laboratory of Bacterial Products, and Dr. Harry L. Smith, Jr., of Jefferson Medical College of Philadelphia, conducted a 3-week bacteriological investigation in the Philippines during the recent outbreak there of "choleriform enteritis."

While in Manila, these two investigators worked closely with the NAMRU–2 team which had also been called to the Philippines to work on the epidemic, particularly on therapy. Part of the support for Dr. Smith came from the SEATO–NIH cholera research fund.

The principal objectives of the study were to field test certain new procedures for the isolation and identification of *Vibro cholerae* and to collect strains of vibrios and sera for future microbiological and serological studies. An incidental but important objective was to make available to bacteriologists in the Philippines, by demonstration and instruction, the new techniques and to help them improve their laboratory procedures.

Using the improved taurocholate gelatin agar medium, the American investigators were able to obtain positive isolations of *Vibrio cholerae* three times as frequently from given specimens as were their Philippine colleagues employing the methods in general use. The new procedures for the rapid identification of *Vibrio cholerae* were found valuable. These consisted of the preliminary identification of colonies of *Vibrio cholerae* by the "string" test (stringiness produced by release of viscous materials from vibrios by bile salts) and a final serological identification with four special sera which serve for groupings and specific typing of the organism.

Following a short period of work and demonstration, most of the local bacteriologists adopted the new methods and accepted supplies of the special antisera.

In addition to obtaining valuable experience with these methods, the 2 investigators brought back to this country for more detailed study some 500 cultures of *Vibrio cholerae* and about 200 sera, including 50 pairs, obtained from cholera cases.

AFRICAN MINISTERS OF HEALTH VISIT DBS LABORATORIES

The Ministers of Health of four of the new African nations visited the Division of Biologics Standards in July, primarily to discuss recent developments in immunization against measles. They also conferred with scientists of the National Institute of Allergy and Infectious Diseases regarding the research programs in tropical diseases, particularly the newer methods for treatment and control of schistosomiasis, onchocerciasis, and malaria.

The four ministers—Dr. Rene Deroux of Dahomey, Dr. Amadou Kone of the Ivory Coast, Dr. Harou Kouka of Niger, and Dr. Paul Lambin of Upper Volta—emphasized that the mortality rate for measles in their countries often reaches 50 percent.

The Division of Biologics Standards staff reviewed the course of natural measles in this country, the symptoms induced in susceptible children by the current experimental live attenuated measles vaccine (Enders' attenuated Edmonston strain), and the new information concerning the essential lack of significant disease induced by the attenuated vaccine in children who also receive immune gamma globulin, although solid immunity to natural infection is induced by the procedure. This finding on the combined use of gamma globulin and attenuated measles virus is a significant development since it advances by several years a method of immunization against measles which can be generally used in the United States.

The study on combined immunoprophylaxis against measles was made by Dr. Fred R. McCrumb and his colleagues, of the University of Maryland, with grant support from the National Institutes of Health, and was reported in the June issue of the American Journal of Diseases of Children.

While combined live attenuated virus and gamma globulin shows great promise for immunizing children in the United States, this method has limitations when employed in developing countries where gamma globulin is in short supply.

The African Ministers of Health indicated that the natural disease in their countries is so severe that they would be willing to accept the moderate illness induced by the attenuated strain when administered without gamma globulin in order to reduce measle deaths.

Dr. Paul Lambin of Upper Volta expressed a desire to undertake with American colleagues a small study to insure that the attenuated measles vaccine which induces a mild illness in healthy American children would not produce a more severe disease in the African children, many of whom have their health impaired by nutritional and parasitic diseases. Exploration is underway to determine whether staff members of the Division of Biologics Standards might participate in such a study, the results of which could have general applicability in many developing countries.

MEASLES IMMUNIZATION PILOT STUDY IN AFRICAN CHILDREN

Three Division of Biologics Standards virologists left in November for Upper Volta, Africa, to conduct a pilot study in measles immunization among children in Ouagadougou. The purpose of this study was to determine the effect of live attenuated measles vaccine in children of Upper Volta where mortality from measles is report to reach 50 percent in the 1- to 4-year-old group. Members of the group were Dr. Harry M. Meyer, Jr., Dr. Daniel Hostetler, and Mrs. Barbara C. Bernheim, all of the Laboratory of Virology and Rickettsiology.

Plans for the study were initiated in July during the NIH tour of the African Ministers of Health. Dr. Paul Lambin, the Minister of Health of Upper Volta, expressed the desire at that time to undertake with American colleagues a small study to insure that the attenuated measles vaccine which induces a mild illness in healthy American children would not produce a more severe disease in the African children, many of whom have their health impaired by nutritional and parasitic diseases. The number of deaths among children in Upper Volta attributable to measles (reported to be about 50 percent), when arranged by age, forms a bell-shaped curve with the maximum mortality occurring at about 3 years.

The children in the pilot study will be immunized by the two procedures now being used in this country: with attenuated virus vaccine alone with attenuated virus vaccine given along with gamma globulin. A third group, serving as a control, will receive only gamma globulin.

Children of two different age groups will be inoculate with the three types of material—one group from 9 to 18 months old who are still being breast-fed and should be nutritionally equal to American children of the same age; the other group from 2½ to 3 years of age who are likely to be suffering from over or subclinical nutritional dificiencies.

After vaccination, the children will be examined periodically for the first 2 weeks, and at 4 weeks a final blood specimen will be obtained from each child. Serologic tests for measles antibodies on the pre- and post-immunization blood samples will be performed in the Division of Biologics Standards laboratories when the team returns in early January.

It is hoped that this pilot study will furnish information that can be used as a guide for later mass immunization of children in such areas.

INTERNATIONAL CONFERENCE ON MEASLES IMMUNIZATION AT NIH

The worldwide problem of measles was presented in a 3-day conference in November at the Clinical Center Auditorium. The conference was jointly sponsored by the University of Colorado, the National Institute of Allergy and Infectious Diseases, and the Division of Biologics Standards, under the chairmanship of Dr. C. Henry Kempe, professor and head of the Department of Pediatrics, University of Colorado Medical Center.

The six sessions covered the worldwide epidemiological aspects of measles; properties of attenuated measles virus strains; field data on the use of live attenuated vaccines; problems of production of the vaccines and biologic control: and the future of measles immunization. Eighty virologists from 22 countries in Europe, Africa, Asia, South America, Australia, and the Middle East presented their data.

The Conference was opened by Surgeon General Luther L. Terry of the Public Health Service who welcomed the guests and paid tribute to the work of Dr. John Enders, who developed the tissue culture methodology which made the propagantion of measles virus possible. The Edmonston strain of measles virus, which has been successfully attenuated through serial passage and has been used in much of the measles research in recent years, was isolated in Dr. Enders' laboratory.

Concerning the measles vaccine, Dr. Terry said, "the next 3 days, I feel certain, will establish the basis upon which recommendation for a safe and effective vaccine can be evolved. It would be an extremely satisfying moment, if I could at this time give a precise answer to the question, 'When will this vaccine become a reality?' but past experience with other immunizing agents forces us to be cautious. It would be foolish and profitless at this time to make any prediction concerning a commercially produced vaccine."

CLINICAL CENTER—HIGHLIGHTS OF PROGRESS IN RESEARCH AND PROGRAM DEVELOPMENTS, 1961

RELATIONSHIPS WITH PRACTICING PHYSICIANS

The clinical center is completing its ninth year as the integrated laboratory-clinical care component of the intramural research programs of the seven institutes. The pursuit of excellence in patient care and the significant contributions to selected areas of clinical investigation have resulted in growing professional prestige. The mutual respect and confidence in the collaborative relationships between the clinical center and thousands of practicing physicians who refer patients from all parts of the United States for participation in the various projects is a significant advance in prevailing attitudes toward governmental activities in medical research.

DEVELOPMENT OF RADIOACTIVE PHARMACEUTICALS FOR DIAGNOSIS AND TREATMENT

The professional advice of the pharmacy department of the clinical center is frequently sought by other hospitals. Commercial pharmaceutical manufacturers also maintain a continuing liaison with the department concerning the development of new drugs and techniques. This is especially true of the Radiopharmaceutical Service in the preparation of investigational types of radiopharmaceutical products.

IODINE 131 LABELED POLYVINYLPYRROLIDONE FOR PARENTERAL USE

The use of this radioactive macromolecule in the diagnosis and study of protein-losing gastroenteropathy has been noted in numerous foreign and domestic publications during the past 3 years. Until quite recently, this research compound had been prepared only by the Radiopharmaceutical Service and distributed free of charge to cooperating investigators, both foreign and domestic, by the National Heart Institute. Consultations with representatives of the United Kingdom Atomic Energy Authority at the Radiochemical Centre, Amersham, England, and with similar representatives of the radiopharmaceutical industry in the United States have now resulted in this product being made available to qualified clinicians in Europe by the Radiochemical Centre and in this country by a domestic manufacturer on a routine commercial basis.

CHROMIUM 51 LABELED HUMAN SERUM ALBUMIN (HSA)

HSA has been successfully labeled with the radionuclide Cr^{51} and formulated into a parenteral dosage form for use by National Cancer Institute investigators in the study of protein-losing gastroenteropathy. This compound has an obvious advantage over labeled polyvinylpyrrolidone in that it is indeed a normal body protein, while polyvinylpyrrolidone is a biologically inert molecule. Representatives of the radiopharmaceutical industry have consulted with the Radiopharmaceutical Service concerning the methods of labeling and formulation of this material employed by the Service, and, through these consultations, this compound too will soon become available to clinicians throughout the world through commercial channels.

KYPTON 85 INJECTION

The pharmaceutical formulation of this radioactive gas into a dosage form suitable for intravenous use in the diagnosis and quantification of cardiac shunts has been a continuing project of the Radiopharmaceutical Service since 1958. While this product has been prepared for intramural use at the NIH, numerous cardiologists and heart surgeons have been instructed by the Radiopharmaceutical Service staff in the method of preparation of this compound in order that this procedure might then be utilized in other hospitals in which these clinicians will be practicing. In addition, many visiting scientists and representatives of the radiopharmaceutical industry have consulted with the Service in the technology of production of this diagnostic agent. Indeed, one company has indicated a readiness to supply this material commercially to interested investigators throughout the country.

IODINATION OF PLASMA PROTEINS

The turnover and metabolic fate of certain plasma proteins is of great interest to investigators at the NIH. While the literature indicates methods of iodinating many of these proteins, not in all cases do these reports indicate that the labeled compound behaves similarly with its nonradioactive biological counterpart. This Service at the present time, in cooperation with investigators in NCI, is iodinating several such compounds which, in general, have been shown to exhibit biological half-lives equivalent to the normal protein in vivo. Extensive research into the technology of these procedures is currently underway within the laboratories of the RPS and the NCI.

ADVANCEMENT OF TELEVISION AND OTHER TECHNIQUES IN DIAGNOSTIC RADIOLOGY

One of the outstanding events of the diagnostic X-ray department during the past year was that of the installation and operation of a radiographic unit embodying image intensification and television monitoring of fluoroscopic procedures. This unit also provided a source for securing cineradiographic films. This new radiographic film has widened the scope of diagnostic X-ray procedures by the Department. It has facilitated a team approach to special diagnostic procedures, such as the performance of needle biopsies of the kidney under direct television fluoroscopic viewing. The unit has also permitted the motion picture filming of numerous physiologic processes such as the acts of phonation and deglutition, and the functioning of the genito-urinary tract.

Another significant advance made by this Department during the past year was the assumption of a more active role in the performance of special radiographic procedures requiring minor surgical skills such as femoral arteriograms, gynecograms, pneumoencephalograms, cerebral arteriograms, etc.

Another highlight in the departmental operation was that of the initiation of the X-ray technician training school in March 1961. This training program will appreciably assist the Department in the future in the employment of suitably trained technical personnel. This training facility will also be of service to the community as there is a real shortage in training programs in the area for student X-ray technicians.

Utilizing image intensification, it has been possible during the past year to significantly reduce radiation exposure to patients undergoing such procedures as the passage of Rubin tubes, Rehfuss tubes, etc. Furthermore, this unit has provided a remote viewing area which can be seen by all physicians involved in the procedures. Thus, it is now possible at all times for the physicians concerned to know exactly where the various tubes are located within the G.I. tract and to determine the exact level at which the small bowel biopsies or small bowel aspirations are performed.

DETERMINATION OF BLOOD VOLUME BEFORE, DURING AND AFTER SURGERY

The accurate determination of blood loss during prolonged surgical procedures has long been a crucial problem for tens of thousands of patients each year. The utilization of modern laboratory techniques for rapid, accurate measurement of blood volume has continued to be a significant activity of our surgeons and anesthesiologists, in cooperation with the NIH Instrument and Engineering Staff of the Division of Research Services. Moreover, during the past year studies have been directed toward the use of a method by which the patient's blood volume can be determined before, during, and immediately following surgery, in order to allow blood replacement to be kept apace with blood loss. These pilot studies, involving the use of a radioactive tracer substance (chromium 51) to tag red blood cells, have progressed here and in several other medical centers to the stage of early use as a routine by anesthesiologists.

WHAT IS RESEARCH TODAY BECOMES ROUTINE TOMORROW

The role of the laboratory is becoming progressively more essential to the conduct of clinical research and the practice of modern medicine. The highly trained physician of this era is not only skilled in selecting, utilizing, and interpreting complicated laboratory tests for following the progress of his patient and in learning of disturbances in delicately balanced states, but he is dependent upon the laboratory in bringing the best medical care to the patient, and in extending the horizons of health. This, then, demands that the accuracy and the reliability of such tests be of extremely high order. Furthermore, in addition to precision, there must be speed. In this research hospital in addition to precision and speed, there is need to develop new tests to meet the new deeds demanded in the constantly varied attempts to unravel the complicated skein of those unknowns which, if resolved, will lead to new knowledge on health problems.

The introduction of powerful new cancer chemotherapeutic agents, requires frequent blood analyses for appraisal of possible toxic effects. Yesterday, these analyses were in the research stage; today they are essential to the adequate practice of chemotherapeutic medicine. Thus, the additive effects of progress become apparent, and since very little of the research in developing new laboratory procedures results in substitutive tests, a 7-percent increase in the volume of laboratory tests occurred in fiscal year 1961.

One of the most pertinent examples of "research today—routine tomorrow" is the striking increase in the need for a greater variety of reliable laboratory tests. This does lead to the reevaluation of the usefulness of contemporary tests, to improved quality control of current procedures, to the automation of equipment wherever possible, and to new approaches to the correlation of laboratory data. It is hoped that through the use of computer analyses, we may be able to "foresee" significant health events which may be depicted in the changing interrelationships which can take place between a variety of chemical values which are still within "normal" limits. In this connection, the recent completion of a new direct digital readout colorimeter, designed and developed in collaboration with consulting electronic engineers, may constitute a significant contribution by the clinical center to the automation of laboratory procedures. At the present time it speeds up the process of colorimetry threefold through making both the readings and the calculations, and recording the results, all in a thoroughly reproducible fashion. While this is of great help to the laboratory, the potential values of feeding these results into a computer for central recording, storage, and pattern analysis are about to be realized, and should be of tremendous significance.

A noteworthy recent development is a dual analytical method to measure both blood sugar and urea nitrogen simultaneously on the same sample. This valuable shortcut has application to the patient, too, since it reduces the amount of blood which must be drawn for test purposes.

BACTERIOLOGIC VIGILANCE

An interesting illustration of the advantages of "cross-fertilization of ideas" in the proximity of various disciplines of research and "routine service staff" is the surveillance of operating rooms, complicated surgical equipment (e.g., heart-lung machine), patients with acquired infections, possible staff "carriers," and general hospital sanitation. Cooperative studies by the Committee on Infections, Department of Clinical Pathology, sanitary engineers, nurses, and others have resulted in stricter procedures for care of complicated surgical equipment, periodic bacteriologic culture surveys of selected patient-care staff members, and greater sensitivity to institutional cleanliness. Continuing studies in the nationwide problem of "hospital infections" have led to the decision to reorganize the clinical center housekeeping activities in a department of hospital sanitation, under the direction of a qualified environmental engineer.

THURSDAY, FEBRUARY 8, 1962.

NATIONAL CANCER INSTITUTE

WITNESSES

DR. KENNETH M. ENDICOTT, DIRECTOR, NATIONAL CANCER INSTITUTE

DR. DAVID E. PRICE, DEPUTY DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DR. G. BURROUGHS MIDER, DIRECTOR OF LABORATORIES AND CLINICS

RICHARD L. SEGGEL, EXECUTIVE OFFICER

DR. LUTHER L. TERRY, SURGEON GENERAL

JAMES F. KELLY, DEPARTMENT BUDGET OFFICER

Object classification

[In thousands of dollars]

		1961 actual	1962 estimate	1963 estimate
	PUBLIC HEALTH SERVICE			
11	Personnel compensation:			
	Permanent positions	$7,127	$8,414	$8,975
	Positions other than permanent	419	390	397
	Other personnel compensation	110	103	188
	Total, personnel compensation	7,656	8,907	9,561
12	Personnel benefits	789	909	965
21	Travel and transportation of persons	400	766	837
22	Transportation of things	73	40	48
23	Rent, communications, and utilities	194	183	186
24	Printing and reproduction	147	187	190
25	Other services	24,291	31,188	31,000
	Payment to—			
	"National Institutes of Health management fund"	6,853	8,484	9,106
	"Bureau of State Services management fund"	25	41	55
26	Supplies and materials	1,429	1,003	1,006
31	Equipment	661	1,078	1,014
41	Grants, subsidies and contributions	62,563	73,816	84,210
42	Insurance claims and indemnities	47		
	Subtotal	105,128	126,600	138,176
	Deduct quarters and subsistence charges	19	20	20
	Total, Public Health Service	105,109	126,580	138,156
	ALLOCATION TO VETERANS' ADMINISTRATION			
11	Personnel compensation:			
	Permanent positions	470	658	689
	Positions other than permanent	96	100	100
	Other personnel compensation	2		
	Total, personnel compensation	568	758	789
12	Personnel benefits	38	53	56
21	Travel and transportation of persons	60	70	70
25	Other services	6	4	4
26	Supplies and materials	27	25	25
31	Equipment	99	95	61
	Total, Veterans' Administration	798	1,005	1,005
	Total obligations	105,906	127,585	139,161

Personnel summary

	1961 actual	1962 estimate	1963 estimate
PUBLIC HEALTH SERVICE			
Total number of permanent positions	1,351	1,423	1,491
Full-time equivalent of other positions	76	64	65
Average number of all employees	1,200	1,371	1,456
Number of employees at end of year	1,328	1,411	1,469
Average GS grade	6.4	6.8	6.9
Average GS salary	$5,876	$6,060	$6,071
ALLOCATION TO VETERANS' ADMINISTRATION			
Total number of permanent positions	89	118	118
Full-time equivalent of other positions	16	16	16
Average number of all employees	95	124	129
Number of employees at end of year	92	128	134
Average GS grade	5.0	4.9	4.9
Average GS salary	$4,857	$4,790	$4,790

Program and financing

[In thousands of dollars]

	1961 actual	1962 estimate	1963 estimate
Program by activities:			
1. Grants and related contracts:			
(*a*) Research	$48,826	$56,936	$65,830
(*b*) Fellowships	1,737	3,100	3,100
(*c*) Training	7,040	7,780	7,780
(*d*) State control programs	3,314	3,500	3,500
(*e*) Community demonstration projects	1,695	2,500	4,000
Total, grants and related contracts	62,612	73,816	84,210
2. Direct operations:			
(*a*) Research	12,693	15,094	16,038
(*b*) Collaborative studies	27,717	34,229	34,341
(*c*) Professional and technical assistance	1,025	1,296	1,836
(*d*) Review and approval of grants	1,188	1,518	1,735
(*e*) Administration	541	893	949
(*f*) Cancer research facility	8	640	52
Total, direct operations	43,172	53,670	54,951
Total program costs [1]	105,785	127,486	139,161
Change in selected resources [2]	122	99	
Total obligations	105,906	127,585	139,161
Financing:			
Comparative transfers to other accounts	356		
Unobligated balance brought forward		−692	−52
Unobligated balance carried forward	692	52	
Unobligated balance lapsing	4,046	15,797	
New obligational authority	111,000	142,742	139,109
New obligational authority:			
Appropriation	111,000	142,836	139,109
Transferred to "Operating expenses, Public Buildings Service," General Services Administration (75 Stat. 353)		−94	
Appropriation (adjusted)	111,000	142,742	139,109

[1] Includes capital outlay as follows: 1961, $581,000; 1962, $1,007,000; 1963, $1,075,000.

[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1960 ,$996,000; 1961, $1,118,000; 1962, $1,217,000; 1963, $1,217,000.

Mr. FOGARTY. Dr. Endicott, you are next.

Go right ahead, doctor.

GENERAL STATEMENT

Dr. ENDICOTT. Mr. Chairman, I have an opening statement which I should like to submit for the record.

Mr. FOGARTY. All right, we will put that in the record at this point.

Dr. ENDICOTT. I will summarize it for the committee.

(The statement follows:)

STATEMENT BY DIRECTOR, NATIONAL CANCER INSTITUTE, PUBLIC HEALTH SERVICE, ON NATIONAL CANCER INSTITUTE

Mr. Chairman and members of the committee, last year I told the committee how the National Cancer Institute was being reorganized to deal more effectively with a broad range of problems and devote more of its resources to the study of cancer in man. I welcome the opportunity to discuss this aspect of our current research program, for study of cancer in man has become increasingly promising in recent years.

The committee is aware that 1962 marks the 25th anniversary of the National Cancer Institute Act. In 1937 our great need was to learn more about the nature of cancer. Consequently, the main emphasis was on experimental research in the laboratory to study cancer in animals and develop new equipment and techniques of refinement and specialization. These studies were intended primarily to gain knowledge of how cancer originates, how it progresses, and how it affects the organism it attacks.

This type of basic research continues to be extremely important, because we have not yet learned the ultimate secrets of the malignant process. Moreover, much of what we still have to learn through experimental research will undoubtedly prove to be of the utmost importance in clinical research.

In earlier years the study of cancer directly in man presented many difficulties. Nevertheless, human population studies yielded significant data on the nature and distribution of cancer and day-by-day clinical observations of physicians dealing with patients led to most of the methods of treating cancer that are in use today.

As time went on, and particularly in the last decade, the study of cancer in man became not only more urgent, but more promising. It became more urgent as findings in the laboratory became more suggestive of profitable approaches to the human problem. It became more rewarding and promising as these approaches began to yield results which could be used as the basis for more penetrating studies.

We are now equipped to give increasing attention to the study of cancer in man. We have acquired the techniques and instruments with which to work, we have developed a sound working partnership between laboratory and clinical investigators—in fact, we have attained a degree of sophistication in research which puts us in good posture to strike the blows that we all hope will give us the ultimate victory over cancer.

These are the developments that have guided the evolution of some of our present and proposed program areas, which I would like to present in some detail. The pattern of large-scale study of cancer in man, which was well established in the chemotherapy program, is not only being continued in that area, but is reflected also in research now in progress on combination therapy, in radiotherapy clinical trials which are just beginning, and in the virus-cancer studies which will undoubtedly become possible before long. This important contribution of the chemotherapy program to clinical research may ultimately be of as great importance as the discovery of drugs for the cure of cancer.

As the committee is aware, the chemotherapy program has developed a broad program of clinical evaluation in which both new and known materials have been studied in thousands of patients. The design and conduct of these clinical trials, and the manner in which they are integrated with the whole national, cooperative chemotherapy program, have taught clinicians in hospitals throughout the country how to deal with drug evaluation in a truly scientific manner. This has been done through carefully designed protocols, controls, statistical techniques, and other steps prerequisite to definitive results concerning specific modes of treatment. Of particular importance is the fact that physicians and other scientists working as teams have learned how to devise definitive, statistically valid clinical studies, and in their day-to-day interchanges of information have stressed uniform study methods and objective criteria and measurements. The end results program permits us to determine, through long-term followup, which forms of treatment have been effective.

As I have indicated, we have been greatly expanding our support of clinical studies. We will continue to do so in the areas of chemotherapy, radiation, and surgery, and in combinations of these modes of treatment. Because of the obvious implications for human studies, we are intensifying our efforts in cancer virology. We are extending our virus studies to cancer patients and human population groups. Studies in cancer diagnosis, carcinogenesis and radiation biology, involving population groups are being interwoven with laboratory research.

I should like, now, to discuss in more detail the following aspects of our program: (1) Clinical studies, (2) virus studies, and (3) field studies.

CLINICAL RESEARCH

Chemotherapy research

The chemotherapy program is still identifying increasing numbers of drugs suitable for trial in man. I would like to mention here some of our cooperative clinical studies. These have been going on for several years, but last year were reorganized to provide for broad-spectrum investigation of new drugs against virtually all forms of malignant disease. This is in contrast to the former method of doing intensive research on compounds against selected forms of cancer. The new approach has been accomplished through the establishment of three new regional cooperative groups, eastern, central and western, which will conduct studies involving as many as 6,000 patients a year.

Out of these cooperative studies have come many significant developments. The committee will be interested, I am sure, in hearing about some of the more important ones.

As you know, one of the standard agents for the treatment of advanced breast cancer is the male sex hormone called testosterone propionate. About 25 to 30 percent of patients who receive this drug experience objective response to it: that is, the spread of their disease is halted temporarily, the size of the tumor itself is reduced, and the need for painkilling drugs is minimized. However, this potent male hormone produces masculinizing effects that are often so distressing to the female patient that the treatment has to be abandoned. A new compound has been developed which has virtually the same anticancer action as the other but is much less masculinizing. This new agent is now available on prescription and is coming into progressively wider use. Such rapid development of a new agent might not have been possible were it not for the national chemotherapy program.

Next I would like to make a progress report on the combination surgical and drug treatment of breast cancer described to the committee last year. Patients treated both surgically and with the drug, thio–TEPA, are still showing a lower rate of recurrence than those treated only with surgery. Now, 3 years after treatment, only one-fourth of the women who received the drug had reappearance of disease, as compared with almost half of those treated only by surgery. We have observed that surgeons are showing an increasing interest in the use of drugs in combination with surgery in their practices.

I should not fail to mention here a very interesting study at the National Cancer Institute, which, although not one of the cooperative chemotherapy projects, nevertheless involves a drug which will probably be scheduled in the near future for clinical trial in the program.

Preliminary results of tests by Institute clinical investigators show that the drug, known by the short name of methyl–GAG, has induced complete remissions in 9 of 13 acute myelocytic leukemia patients, 5 of whom have remained in remission for periods up to 5 months. This type of leukemia comprises about 85 percent of all acute leukemias in adults, and about 15 percent in children. Without treatment, half of all acute leukemia patients die within 2 to 3 months. The best drug until now available usually induces complete remissions in only 1 in 7 patients. The average remission has been 10 months in adults; thus, several months will have to pass before we shall have a more definite impression of the efficacy of this new drug. Methyl–GAG was synthesized by Ben L. Freedlander and Fred A. French at Mount Sinai Hospital in San Francisco, and is made for the Cancer Chemotherapy National Service Center by Riker Laboratories of Northridge, Calif.

Radiation research

The Institute's program of radiation therapy research and training approved by the Congress last year is designed to encourage basic and clinical research. It will support, too, the training of urgently needed skilled professional and technical radiotherapy personnel, and stimulate the development of comprehensive radiation therapy programs in medical schools and teaching hospitals in which skilled personnel, patients, and advanced facilities will be concentrated. A start has been made this year utilizing research grants, center grants, and training grants.

Following the prototype studies in chemotherapy clinical trials, cooperative groups are using combination radiation-surgery and chemotherapy approaches. The following developments are worth citing:

Excellent results of radiation and drug treatment of Hodgkin's disease in adults have been reported. Advanced disease is treated by an alkylating agent such as nitrogen mustard and then by radiation. Localized and regional disease treated by radiation alone seems to be yielding cures. A significant percentage of children with retinoblastoma, a malignant eye tumor, who were treated with radiation and an alkylating agent, TEM, were living without disease and with a hopeful outlook for useful vision 4 years after completion of treatment. Treatment of Wilms' tumor, a cancer of the kidney in children, was strikingly effective when an antibiotic actinomycin-D was used in combination with radiation. In treatment of both retinoblastoma and Wilms' tumor, the doses of radiation in combination with drugs were smaller than those required when radiation was used alone.

Our imagination has been seized by some recent radiobiologic findings in this area. These have shown that human cells growing in tissue culture can incorporate small amounts of chemical compounds known as halogenated pyrimidines without impairing the biological functioning of the cell. This class of compounds is relatively new in chemotherapy; two of its members, 5–FU and 5–FUDR, are quite familiar to the committee and show some activity against cancer of the colon and rectum when given in relatively large doses. The importance of these compounds for radiation therapy is that they markedly enhance the radiosensitivity of the cells. The implications with respect to cancer therapy are obvious. It is hardly necessary to say that intensive work has progressed to a point where early clinical trials of the sensitization of tumors to radiation are underway.

The implications with respect to basic knowledge of the mechanism of radiation injury to living matter—a problem of vital importance because of the increasing radiation hazards in the environment—are equally profound. The findings provide the most convincing evidence yet obtained that the radiosensitive sites in cells are indeed the genetic material, or more precisely the nucleic acid called DNA.

VIRUS RESEARCH

The possibility that some if not all forms of cancer in man may be caused by viruses, and that these viruses may be rendered inert by immunization or destroyed by drugs is one of the most exciting prospects before us. What makes this so intriguing is that it could bring under definite and effective control, through prevention or treatment, whole categories of malignant disease, such as leukemia, which now are either invariably fatal or poorly responsive to the best treatment devised.

Viruses and human cancer

The committee is well aware, of course, that we are moving into virus-cancer research with the human problem in mind because of the mounting undisputed scientific evidence that many cancers in animals are caused by viruses. As in other areas of research, these lines of investigation all point, sooner or later, toward the human cancer target. I know that you are, therefore, anxious to learn how the evidence in the case is building up and what we propose to do about it.

The staging operations for this activity have gone forward during the year in both the intramural and extramural areas. A year ago I referred in general terms to the things we wanted to accomplish and indicated, so far as I was able, what needed to be done to realize these objectives. In the intramural area we have established a Laboratory of Viral Oncology and transferred to it the personnel and resources from other laboratories where important work related to this field has been going on for years. We have allocated a large share of responsibility for the total virus-cancer research approach to this group, and already they have developed some exciting leads. One turned up when an electron microscope study revealed characteristic virus particles in the blood of rats bearing a virus-induced leukemia. The scientists who participated in this work went on to design a relatively simple scheme for extracting essentially pure virus by spinning the blood at high speeds in a centrifuge. Their success raised the prospect of finding viruses that may cause human leukemia by applying the same technique to blood from leukemia patients. Several Institute scientists are now collaborating in this very project. They are obtaining blood specimens from patients undergoing treatment at the Clinical Center of the National Institutes of Health and from others living in areas where clusters of leukemia cases have occurred. We are exploiting this line of research as rapidly as we can.

To expedite the work involved in testing specimens from cancer patients, we are enlarging certain facilities in the Laboratory of Viral Oncology and introducing a number of innovations. The latter include virus preparation and diagnostic units and a pathology and hematology unit, which will handle the routine operations that make up a considerable share of the work. Two new electron microscopes have been purchased for use in screening human specimens for evidence of virus. Without this means of selection, the number of specimens that would have to be tested biologically would far surpass the number the Laboratory can handle. We have also made a contract with a commercial laboratory for the production and housing of approximately 22,500 newborn mice. These animals will be observed for at least 18 months after they have been inoculated with human extracts.

Possibilities in prevention

The investigation of viruses in relation to human cancer must be based on what is learned about viruses and cancer in animals under experimental conditions. Large amounts of pure viruses are needed for study of the natural history of the disease in animals and the biochemical action of viruses on the reproductive mechanism of cells. To meet this requirement we have entered into contract with a commercial laboratory for the production of large quantities of animal leukemia viruses in tissue culture.

There is a possibility that a vaccine against virus-caused animal cancer may emerge from such large-scale laboratory operations. This would be of great importance in the event that even one form of human cancer should prove to be caused by a virus. No one knows when this may come about, but the status of research in this field makes it imperative to anticipate such a development at any time. Therefore the skills acquired in producing viruses in tissue culture will make it possible to move more rapidly into vaccine production when the need arises.

Should human cancer viruses become available, the quantities required for large-scale vaccine manufacture could probably best be produced in tissue cultures of mammalian cells. In doing so it is important that the tissue cultures be free of other viruses. Such viruses are easily introduced into tissue cultures by animal sera often needed in the nutrient if cells are to grow. Our intramural scientists have been successful in growing seven cell types in chemically defined media free of animal extracts. Different cell types require their own recipe of nutrient in which to grow. We are anticipating contracting with a commercial concern so that in as short a time as possible we will have a greater variety of cell strains growing in chemically defined media in mass quantities. If successful we will then be able to select the particular cell type most suitable for growing suspected tumor viruses without likelihood of contamination.

Encouragement for research

With the establishment of the Virology Research Resources Branch last August, steps were quickly taken to stimulate nationwide and worldwide collaborative research on viruses as a cause of cancer. The Branch undertook immediately to provide essential materials and services to all scientists working in this field, in which support for research reached a level of $6,500,000 representing 175 grants.

Several mammalian cell lines whose characteristics and purity were certified under the auspices of the program are now ready to be deposited in the cell bank operated by the American Type Culture Collection. These seed stocks will be delivered on request to qualified investigators for use in tissue culture work. Viral identification reagents produced under contract are already being distributed. Work has been started on the development of mice whose virus population is fully known, and efforts to develop a similarly virus-defined primate are being planned. In addition, plans are in progress for establishment of a tissue bank, which will store normal and malignant human tissues and serum samples from patients with many forms of cancer. This Institute is working closely with the National Institute of Allergy and Infectious Diseases in providing and distributing diagnostic reagents. NIAID is assuming responsibility for providing services and materials needed for investigations on human viruses in general. National Cancer Institute has direct responsibility for research on viruses as a cause of cancer.

The properties of viruses

Certain other aspects of virus-cancer research are equally interesting and important. As I have indicated, we are alerting every resource to the possibility of developing a vaccine to render human cancer viruses harmless should they be discovered. There is also the possibility of modifying these viruses by means of biochemical techniques, and this is unquestionably a highly attractive prospect. For this reason we are continuing our longstanding interest in building a fund of basic information about the properties of viruses and their reactions to chemical treatment. The fact that medical science has not as yet produced an effective treatment for any human viral disease does not deter us, and we are considering, in fact, the advisability of undertaking active research in this field under the chemotherapy program.

The possibility of attacking cancer viruses chemically is suggested by the work of scientists at the National Cancer Institute and elsewhere who are manipulating viruses and their component parts in the laboratory. Some of this work is interesting to report. There is now a great deal of evidence that viral nucleic acids alone can produce the same effects caused by infection with complete viruses. One of the more recent contributions has come from Cancer Institute grantees at the University of Washington. They have shown that nucleic acid extracted from a virus that induces a skin tumor in rabbits will also induce such tumors.

Scientists in the Institute's Laboratory of Biochemistry have been studying ways of determining the order in which thousands of chemical units are arranged in nucleic acid molecules. By mixing nucleic acids with enzymes that split them at certain places, these investigators break the molecules into pieces which can be analyzed. In this way, the arrangement of a few units can be deduced. This approach will soon be applied to studies of the Moloney mouse leukemia virus, isolated three years ago at the National Cancer Institute.

In our Laboratory of Chemical Pharmacology, basic research is being done on ways of inactivating viruses that ordinarily infect bacteria. Such viruses have been found to lose their infectivity when treated with certain negatively charged chemicals. The investigators are now attempting to use the same techniques to inactivate the tumor-inducing polyoma virus.

FIELD STUDIES

Areas of research which deal quite directly with human cancer as a disease entity have been grouped as field studies under the Institute's reorganization.

Cancer-causing agents

In this group we have established a new Carcinogenesis Studies Branch which will carry forward and expand the research conducted by the Institute for many years to identify cancer-causing agents in the environment of our increasingly urbanized and industrialized society. This is a very old and productive area of research which has, in fact, demonstrated that cancer is a preventable disease.

The Carcinogenesis Studies Branch will undertake to perfect bioassay test methods and develop new, more accurate approaches to investigation of agents which are known to cause cancer in animals and are therefore potentially harmful to man. These include elements of pollution in the atmosphere, soil and water, chemicals used in industrial operations and household products, additives in food, food containers, and cosmetic preparations.

One of the most important objectives here is to determine whether there is a threshold effect of such agents so far as human beings are concerned. To facilitate this work grants will be made to establish, develop, and give long-term support to university laboratories entrusted with programs of research and training.

An important aspect of laboratory research on environmental cancer has been to establish the interval between the administration of a cancer-causing agent and the appearance of the resulting tumor in an animal. Efforts have also been made over the years to establish this period of latency in cases of human cancer attributed to exposure to a causative agent. Now we propose to explore with precision the dose-response relationship of representative chemicals from the various major classes of chemical carcinogens. We wish to determine whether there is a threshold dose or not. To conduct studies along these lines, we plan to establish special testing laboratories through research contracts.

Population studies

The work of the Carcinogenesis Studies Branch will have an important relationship to the proposed development of human population laboratories designed to produce more comprehensive information on cancer risks. It is planned to establish these laboratories at institutions with academic affiliations to provide for the training of personnel. Later on, we plan to establish systematic coverage of important population subgroups, and a central liaison group will be formed to coordinate and participate in activating population-based studies. These investigations can be most effectively developed with the active collaboration of laboratory studies to identify and describe the various agents that can cause malignant disease in man.

Continual study of the mode of attack of cancer in populations of different environmental and ethnic backgrounds offers a good potential for new leads. A good example of a research approach of this kind is the large-scale National Cancer Institute study of cancer mortality among the foreign born in the United States. To date we have analyzed more than 34,000 cancer deaths recorded during 1950 for foreign-born white individuals from 12 countries in 35 States. These data showed that in general the foreign born were subject to different patterns of cancer risk than the native white population. The pattern was generally similar to that of the parent which indicates that the factors responsible for carcinogenesis can exert their influence many years after exposure since most of the patients had been away from their native lands for a long time.

Diagnostic research

In dealing with the problem of cancer in man, early and accurate diagnosis is extremely important to management of the disease and to the outcome for the patient. For this reason diagnostic research has long occupied the attention of many scientists in the National Cancer Institute and other research institutions.

As one of the lines of investigation pointing toward the human cancer target, we are rapidly developing a program in the field studies area which is designed to stimulate, extend, and evaluate exploratory and developmental research in the basic and clinical sciences related to diagnosis and prognosis of cancer. To this program we are bringing the resources of funds, personnel, facilities, and ideas, and the opportunity for interested scientists everywhere to participate either by doing research or providing consultation and advice. The Institute's recently established diagnostic research branch will develop as a focal point for the collection and dissemination of information on the status and needs of research in all fields related to diagnostic research. It will administer this broadly based program not only through our own intramural facilities but also through direct operations in other laboratories and under contractual arrangements. The branch will stimulate the whole effort also by sponsoring conferences, symposia, and seminars.

The people of the diagnostic research branch are also watching with keen interest the development of our virus-cancer work both in the intramural program and outside. The resources of the field studies group, particularly those devoted to improvement of diagnosis, are undoubtedly going to be helpful to the virus research effort, especially for population studies. We are interested, for example, in occasional outbreaks of leukemia in certain localities such as in Niles, Ill., where several children who had contact with each other in school or in their neighborhoods developed leukemia at about the same time. Improved diagnostic procedures would help these patients to receive prompt and proper treatment, and would also enable research teams to take best advantage of these situations for study purposes.

From time to time, over the years, investigators have come forward with tests claimed to be useful for the detection of cancer in early stages. For some time the National Cancer Institute supported several large projects to subject these tests to critical field trials. On careful trial, none was found to be reliable. Although the search for a universal test for cancer continues, experts are not optimistic as to the outlook for the development of a reliable one. It appears likely that greater success will be achieved by seeking specific tests for specific types of cancer, and by improving the diagnostic methods already available.

Although the final diagnosis of cancer is still based on microscopic examination of tissue sections, there are many other laboratory determinations which are of great value in reaching a decision that cancer is probably present in a person. These include X-ray and fluoroscopic examination with or without contrast media, measurement of certain enzyme levels in the blood, measurement of certain hormones in the blood and urine, detection of abnormal proteins in the blood and urine, etc. We are broadening our program to include research and development in these various areas.

CANCER CONTROL

In closing, I would like to speak of progress in the cancer control program as administered in the Bureau of State Services of the Public Health Service. The strength of this program lies in its ability to help reduce the serious and costly lag between the findings of research and their application in the routine practice of physicians and health workers throughout the country. A guiding principle in cancer control has long been that the fate of the cancer patient rests to a critical extent in the hands of the first physician he sees. Program activities, therefore, are aimed at alerting the medical profession to new opportunities for early case finding, and expanding and reinforcing the doctor's resources for carrying these out.

At the present time, the greatest potential for prevention and control lies with cancer of the uterine cervix and cancer of the lung.

Over 10,000 deaths still occur annually from cervical cancer despite current knowledge which could prevent nearly all of these. During the past year, 20 community demonstration grants were directly concerned with demonstrating better methods of carrying out cervical cancer case-finding programs. For example, such a project among women receiving welfare benefits in Florida is not only uncovering more than 25 cervical cancers for every 1,000 women examined, it is also identifying many of the obstacles encountered in convincing less-informed women of the value of an annual cervical examination.

To increase the supply of skilled cytotechnicians, grants have been made to 38 schools of cytotechnology. These funds will help train about 180 laboratory technicians. But this is only a start toward producing the 1,200 additional cytotechnologists needed to increase the number of women examined annually from the current 5 to 10 million for effective uterine cancer control.

Since the total amount of funds allocated for grants to State health departments was increased by the Congress last year, it has been possible to make funds available for each State to staff at least a minimum cancer control program. More than 60 percent of the additional funds were budgeted for clinical and case-finding activities and other local health services. More money was also devoted to supporting registry systems to improve patient followup and to augment data on cancer incidence and treatment.

The Public Health Service believes that the evidence regarding cigarette smoking as a major cause of lung cancer is sufficiently strong to justify an intensive educational campaign. Experience with educational campaigns in this field leads us to believe that a key factor is the attitude of physicians and other health workers. Therefore, our educational campaign is directed primarily at these professional groups, while that of the American Cancer Society is concentrated particularly on the lay public.

Operational studies have been undertaken to explore further other potential tools for reducing cancer mortality. As these are developed, the cancer control program will make full use of them to hasten the time when the benefits of research are fully available in communities throughout the country.

CONCLUSION

In conclusion, Mr. Chairman, the request for 1963 of $139,109,000 provides for additional funds in a number of activities.

The largest of these, other than for centrally furnished services discussed elsewhere, are:

(1) An increase of $8,894,000 in research grants will permit us to pay most of the new approved grants including the area of radiation therapy previously outlined. Approximately $1,349,000 of these funds will be used for general research support grants.

(2) An increase of $1,500,000 for additional community demonstration projects in cancer control—an important step in bringing the benefits of research to the people.

(3) An increase of $335,000 for direct research which will permit us to intensify virology studies in our laboratories. Particular attention will be given to the development of chemically defined tissue culture media and the examination of tumor specimens for virus particles.

(4) An increase of $404,000 for field studies will permit expansion of research of cancer-causing substances in our environment and for epidemiology.

(5) An increase of $537,000 for professional and technical assistance will provide professional consultation to help develop new approaches to local cancer control problems and to extend community programs. Other smaller, but no less important, increases are described in the budget document.

Grants and related contracts:	
Research	$65, 830, 000
Fellowships	3, 100, 000
Training	7, 780, 000
State control programs	3, 500, 000
Community demonstration projects	4, 000, 000
Subtotal, grants	84, 210, 000
Direct operations:	
Research	16, 038, 000
Collaborative studies	34, 341, 000
Professional and technical assistance	1, 836, 000
Review and approval of grants	1, 735, 000
Administration	949, 000
Cancer research facility (brought forward)	(52, 000)
Subtotal, direct operations	54, 899, 000
Total 1963 appropriation request	139, 109, 000

Dr. ENDICOTT. Last year I described to the committee ways in which the National Cancer Institute was being reorganized to deal more effectively with the broad range of problems and to devote more of its resources to the study of cancer in man. Today I welcome the opportunity to discuss with you this aspect of our current research program and to present the 1963 budget request of $139,109,000 for the Institute.

OBJECTIVES OF CANCER INSTITUTE STUDIES

The laboratory studies of the Institute's early research were primarily intended to gain knowledge of how cancer originates, how it progresses, and how it affects the organism it attacks. This type of basic research continues to be extremely important, and as we have acquired knowledge, techniques, and instruments, we are now equipped to give increasing attention to the study of cancer in man.

The pattern of large-scale study of cancer in man, which was well established in the chemotherapy program, is not only being continued in that area but is reflected also in research now in progress on combination therapy, in radiotherapy clinical trials, which are just beginning, and in the virus-cancer studies which will undoubtedly become possible before long.

CHEMOTHERAPY PROGRAM

The chemotherapy program is still identifying increasing numbers of drugs suitable for trial in man. Last year our cooperative clinical studies were reorganized to provide for broad spectrum investigation of new drugs against virtually all forms of maligant disease. Out of these cooperative studies are coming many significant developments. One of these is a new compound for the treatment of advanced breast cancer with few of the masculinizing effects of the older drug.

Mr. FOGARTY. What is the name of that?

Dr. ENDICOTT. This is 2 alpha-methyl-dihydrotestosterone propionate. The main drug is testosterone, the male sex hormone.

RADIATION THERAPY RESEARCH

A start has been made in the development of the Institute's new program of radiation therapy research and training approved by the Congress last year. Following the prototype studies in chemotherapy clinical trials, cooperative groups are now using combination radiation-surgery and chemotherapy. Excellent results have been reported in the radiation-drug treatment of Hodgkin's disease in adults. Treatment of Wilms' tumor, a cancer of the kidney in children, has been found strikingly effective when an antibiotic, actinomycin-D, is used in combination with radiation.

Mr. FOGARTY. What is the name of that?

Dr. ENDICOTT. Actinomycin-D.

Mr. FOGARTY. Does that have any relation to streptomycin?

Dr. ENDICOTT. Well, Actinomycin-D actually is one of the earlier antibiotics to be isolated, and it was abandoned for a number of years because of its extreme toxicity. It is one of the most poisonous substances I have ever encountered. And it is used in extremely minute doses. It has a broad spectrum of activity against micro-organisms, but it is so toxic to the host that it is not useful for that purpose.

VIRUS CANCER RESEARCH

The staging operations for virus cancer research have gone forward during the year in both the intramural and extramural areas. Some exciting leads have been turned up by National Cancer Institute scientists working in our Laboratory of Viral Oncology, including the development of a comparatively simple technique for extracting essentially pure virus from the blood of leukemic rats. This technique is now being employed on blood specimens from leukemia patients undergoing treatment at the Clinical Center of the National Institutes of Health, at the institutions around the country, and from others living in areas where clusters of leukemia cases have occurred, particularly from a group of patients and their families in Niles, Ill., where there is an unusual incidence of acute leukemia among the children in one school.

It is still too early to report any results of these studies, but we are very excited about them.

REQUIREMENT FOR EXPERIMENTAL ANIMALS

Virus-cancer research on the scale we anticipate requires large numbers of special experimental animals, large amounts of animal viruses, and a constant supply of normal and tumor cells in tissue cultures.

Last August we established a Virology Research Resources Branch whose primary mission is to develop and make available the special kinds of animals, tissue cultures, experimental materials, equipment, and equipment methods, to tackle this problem in a direct fashion.

VIRAL IDENTIFICATION REAGENTS

Among the early efforts is the large-scale production of viral identification reagents such as antibodies for specific viruses, or the virus itself, for distribution among investigators active in the field.

Now, this work has proceeded very well and during this year we have made arrangements to share the responsibility for this program with the Allergy and Infectious Diseases Institute, which, beginning next year, will take over the responsibility for the production and distribution of the human viruses, while the Cancer Institute will concentrate primarily on the known or suspected cancer viruses.

This transfer of function is reflected in the budget.

CARCINOGENESIS RESEARCH

Several areas of research which deal directly with human cancer as a disease entity have been grouped as Institute field studies. In this group a new Carcinogenesis Studies Branch has been organized to carry forward research on cancer-causing agents in the environment. The work of this branch will have an important relationship to the proposed development of human population laboratories designed to produce more comprehensive information on cancer risks.

As one of the lines of investigation pointing toward the human cancer target, a field studies program is being rapidly developed to stimulate exploratory and developmental research related to diagnosis and prognosis of cancer. The Institute's recently established Diagnostic Research Branch is administering this broadly based program through our own intramural facilities and under contractual arrangements.

CANCER CONTROL PROGRAM

In the cancer control program, whose objective is to reduce the lag between research findings and their application in routine practice, studies have been undertaken to find the best ways of alerting general practitioners to the opportunities for early case finding of cancer of the uterine cervix. This program is also conducting an intensive educational campaign among physicians and other health workers on the risk of lung cancer resulting from excessive cigarette smoking.

SUMMARY OF 1963 BUDGET REQUEST

In conclusion, Mr. Chairman, the request for the National Cancer Institute for 1963 is $139,109,000 as compared with the $126,945,000 available in 1962. The request for 1963 will provide for an increase of $8,894,000 in research grants; an increase of $1,500,000 for additional community demonstration projects in cancer control; an increase of $335,000 for direct research; an increase of $404,000 for field studies; and an increase of $537,000 for professional and technical assistance. Other smaller but no less important increases are described in the budget document.

GENERAL JUSTIFICATION OF CANCER RESEARCH EXPENDITURES

Mr. Fogarty. You apparently feel quite optimistic about the progress that is being made in this field?

Dr. Endicott. Yes, sir; I do.

Mr. Fogarty. What answer do I give someone in Congress when they get up on the floor and say: "Here, we are spending $127 million and we spent so many hundreds of millions of dollars in the last 25 years in research on cancer, and still 260,000 or 270,000 people are going to die of it this year"?

"You still do not know the cause of it or how to cure it."

What is the best thing I can say to a person like that?

Dr. Endicott. Well, I think perhaps that the best answer is that it is a big problem, it is going to cost a lot to solve it.

But I would certainly not want to overlook the fact, in answering such a question, that although 250,000 people will die of cancer, there are a good many who will not, who otherwise would have.

Mr. Fogarty. You have some facts and figures on that?

Dr. Endicott. Yes.

Mr. Fogarty. I was hoping you would give me something a little stronger than that.

Dr. Endicott. The analysis which we completed last year, primarily based on studies in Connecticut, indicate that of cancers which were diagnosed in the early 1930's, the death rate was such that 1 out of 4 persons were cured and 3 out of 4 died.

In the most recent period examined, which is by now 2 or 3 years old, the death rate had changed; the survival rate had improved to the point where 1 out of 3, instead of 1 out of 4, is being cured.

Now, these are——

NEED FOR IMPROVED CANCER CURES

Mr. Fogarty. How many others could be saved if they went to a doctor in time?

Dr. Endicott. This is an estimate, which I believe is true, but of course it is not subject to proof. It is probable that one out of two would be saved if they were brought to the doctor's attention and if he recognized the cancer and treated it adequately early in the disease.

Now, we are still left with a large number of types of cancer for which we really have very poor cure rates, no matter when the patient comes to the doctor. In leukemia, cancer of the stomach, and a number of other malignancies, the cure rate is exceedingly low, even under the best circumstances.

Mr. Fogarty. I knew that about leukemia, but I know people that had stomach cancer 8 or 9 years ago, and they are still around and leading an active life.

Dr. Endicott. Yes. The cure rate for cancer of the stomach is on the order of 5 percent, and it is on the same order for cancer of the lung. They may not have a recurrence for some time.

CANCER OF THE UTERUS

Mr. Fogarty. You have made, I think, dramatic strides in the problem of cancer of the uterus in women.

Dr. Endicott. This is a very good specific example. Here, the surgical results are excellent if the tumor is localized. You can achieve a high cure rate with early diagnosis, and we have a good detection test—the "Pap" smear. A good deal could be accomplished with cancer of the large bowel if we could somehow get people in the susceptible age groups to submit to proctoscopy soon enough so the tumor can be discovered before it spreads.

Mr. Fogarty. What is the age group, the most susceptible age group?

Dr. Endicott. Most commonly after 40, or occasionally before that time. The highest incidence is in the fifties and sixties.

DIAGNOSTIC RESEARCH

Mr. Fogarty. Why have you not been able to develop an easier method of examination?

Dr. Endicott. Well, I think perhaps one of the reasons is that the whole area of diagnosis has lagged in the research field. We have been trying to understand why this is so and do something about it more broadly.

As you know, at the request of the Congress, the Cancer Institute established a special diagnosis research program a few years ago. At first, our approach was more or less on the basis of looking for a general diagnostic test that would work in all cases. We were not able to interest very many people in working in this area, and I think for a good reason, because the prospects, in my opinion, are rather—well, the odds are pretty long. In general——

Mr. Fogarty. What are you going to do about it? Are you going to drift along, or are you going to change directions, or what?

Dr. Endicott. We are going to change directions.

Mr. Fogarty. I remember several years ago being told that this was one of the more difficult areas to work in, and no one who came before us offered much hope. They said it was going to be a long time before new diagnostic tools or methods could be developed. And that is why we gave you additional money and earmarked it for that purpose.

Dr. Endicott. Well, the approach which we think was proper—we have studied this matter very carefully—is to set up the best advisory group that we could find. We believe, as a result of a careful analysis of the situation, that we will get a lot further faster if we attempt to solve the diagnostic problems, cancer by cancer, and not put all of our chips looking for a panacea diagnostic test.

Now, this is easier said than done. You are probably well aware of the fact that the clinical laboratory in hospitals tends to be kind of an orphan. It is usually under the direction of a pathologist whose training is primarily in tissue pathology. Until very recently, there were almost no pathologists whose training had been primarily in clinical chemistry, immunology, bacteriology, hematology, and so on. The profession has attempted——

RHODE ISLAND HOSPITAL CANCER RESEARCH

Mr. FOGARTY. Well, what about an operation like the Rhode Island Hospital? They just built a new building, called the George Building, which was built for the purpose of going into cancer research. And an entire building was designed for it. Would that not be a place where they would strengthen their research activities and not deal with just tissues, but everything?

Dr. ENDICOTT. Yes, sir.

The problem, it seems to us, has been that those who work in the laboratory with cancer, let us say, usually working with animal cancer, often develop interesting new chemical procedures, immunological procedures, and so on; but they are not the people who are concerned with making the laboratory tests in the hospital. And for the most part, hospital laboratories are operated in a rather routine fashion, not by physicians but by technicians.

TRANSLATION OF BASIC RESEARCH

Mr. FOGARTY. What about your own?

Dr. ENDICOTT. Ah, that is one of the things that led me to decide that this was worth exploring more broadly.

The clinical center is fortunate in having one of the finest clinical pathologists in this country. He is very much research oriented, and has in a few years, I think, made enormous strides in translating basic research manipulations from the laboratory into practical tests which can be used on patients on a large scale with a high degree of precision so that one can find out whether these have significance in diagnosis or not. The translation of the laboratory finding into the clinical setting, and its large-scale exploration in a precise and scientific way seems to be the ingredient that is missing.

What we are in the process of doing is identifying the limited number of research-type clinical laboratories that there are in this country, and encouraging them to expand their research, and particularly to expand their training activities, and we are trying to help them create, as Dr. Shannon mentioned this morning in connection with his training program—we are trying to help create a research environment in laboratory medicine.

Now, this will also extend into the field of radiology, because at the present time one of the major diagnostic tools, perhaps second only to the biopsy itself in the detection of cancer, is X-ray. And we believe that a great deal can be accomplished in the field of X-ray diagnosis by stimulation of research and research training in this area, which up to now has been like anesthesiology—one of the fields where we had almost no proposals for research projects.

Mr. FOGARTY. If we had heard that, we could have given you some money to get some started.

Dr. ENDICOTT. This is not going to yield results overnight. In both areas we are starting from a small base.

BREAST CANCER

Mr. FOGARTY. What is the method of diagnosis for breast cancer; just the lump in the breast, is that the only way?

Dr. ENDICOTT. Yes. The diagnosis of breast cancer, unless it has spread to the lungs, let us say, or to the skeleton, in which case you would pick it up by X-ray, almost entirely is based on palpation of the breast, and the diagnosis is usually confirmed in the operating room with frozen-section biopsy.

Mr. FOGARTY. Which is too late many times?

Dr. ENDICOTT. Yes.

The decision then as to whether it is really cancer or not is made in the situation where the woman is made ready for a radical mastectomy. There is a small incision made and a piece of tissue removed and studied under the frozen-section technique, right in the operating room. A decision is then made as to whether it is cancer and the whole breast comes off, or whether it is benign.

Mr. FOGARTY. Off the record.

(Discussion off the record.)

Mr. FOGARTY. All right, let us go back on the record.

Dr. ENDICOTT. In cancer of the breast, we have a study in progress which is a very interesting one. It is an outgrowth of an observation made at the M. D. Anderson Hospital in Houston, Tex. The radiologist there became interested in the possibility of detecting cancer of the breast by taking X-ray pictures of the breast in a number of different shots, using special techniques for soft tissue X-ray, which provide delicate gradations of contrast. He had very good luck in the detecting of cancer of the breast. His batting average was very high as measured by the diagnosis at biopsy. And in a fair number of cases he picked up cancer of the breast that was missed by the examining surgeon.

Now, this happened particularly when both breasts happened to be involved. And the surgeon would detect the cancer mass in one breast but miss it in the other.

Now, we were fascinated by this as a diagnostic possibility, and we have a reproducibility study going on at the present time and are planning a large-scale test of this diagnostic method. We do not know yet which of the groups will finally undertake it, but it will probably be undertaken by one of the big hospitalization insurance groups, like HIP in New York City or perhaps the Kaiser group in California. Then we can apply this on a large scale and explore its possibilities as a population screening technique.

At the moment the X-ray procedure is expensive. But if the test is accurate, with the large pictures, we can probably get enough technical improvements as we did in chest X-rays to screen populations with some less expensive technique.

1963 BUDGET

Mr. FOGARTY. Your appropriation for 1962 is $142,836,000, and the request for 1963 is $139,109,000, a reduction of $3,727,000.

After taking all the adjustments into consideration, your justifications show there will be a cut of $4,221,000 in this budget for 1963. Is that right?

Dr. ENDICOTT. Yes, sir; that is the difference over what the appropriation is.

RESERVE OF 1962 APPROPRIATIONS

Mr. FOGARTY. The reserve is $15,797,000. How much of that is forced savings?

Dr. ENDICOTT. The precise figure is $11,404,000.

Mr. FOGARTY. You have the second largest reserve in the whole Department. And the one that kills the most people was hit the hardest—heart, by over $13 million.

What does the rest of the reserve represent?

Dr. ENDICOTT. The rest of the reserve?

Mr. FOGARTY. The nonforced portion, which is $4,393,000. What does that represent?

Dr. ENDICOTT. It was volunteered as money that we probably would not require.

The bulk of this was in research grants. There were small items in several other areas. $4.3 million for research grants, $33,000 in direct research, $30,000 in review and approval, and $30,000 in administration. That is the total of $4,393,000.

FUNDING APPROVED RESEARCH GRANTS

Mr. FOGARTY. How many approved research grants in 1962 will you have that you will not be able to finance?

Mr. KELLY. The current estimate is 224 for $5,440,266, Mr. Chairman.

Mr. FOGARTY. That is the current estimate?

Mr. KELLY. Yes, sir.

Mr. FOGARTY. That is what appears in the tables we have, but is that the latest estimate you have?

Mr. KELLY. Yes, sir; this estimate was just received from the National Institutes of Health within the last few days. I should point out, however, that it related exclusively to the regular program of project grants, and assumes that the funds for the special research grant programs will be used at the levels at which they are allocated in the budget. This may not be a valid assumption. If, for example, all of the $7.5 million allocated for cancer clinical research centers is not used, the backlog of approved project grants would be greatly reduced or wiped out altogether.

Mr. FOGARTY. If $5.5 million dollars was released from the reserve you could meet these applications that have been approved?

Dr. ENDICOTT. Yes, sir.

Mr. FOGARTY. Do you have demands for the other $6 million if it was released?

PROBLEM DEFINING CLINICAL RESEARCH CENTER

Dr. Endicott. Our picture, sir, is rather confused at this point. What is throwing our estimates off—and I do not know how it is going to come out, frankly——

Mr. Fogarty. What do you mean?

Dr. Endicott. Is that some of the money which we had earmarked for the support of cancer clinical research centers, we now find can not be used due to the definition of what constitutes a clinical research center.

So we will be in a position, I am sure, at the end of this fiscal year of lapsing money for cancer centers.

Mr. Fogarty. Just briefly tell me what the qualifications are?

Dr. Endicott. Well, the specifications which were established——

Mr. Fogarty. By whom?

Dr. Endicott. By the National Institutes of Health.

Mr. Fogarty. You mean the Cancer Institute?

Dr. Endicott. No, the National Institutes of Health, and I must confess that at the time it was done, I was, to a considerable extent, responsible for it because I was wearing another hat.

But be that as it may, the working definition of centers—and this, I believe, was also concurred in by the Congress—describes them as a geographical entity, a cluster of beds in a finite place with, perhaps, an attached laboratory, a diet kitchen, and a staff to operate this small group of beds. And they were conceived of in the first place as facilities in which high-precision studies of the physiology and biochemistry of sick and well people could be carried out with the very highest, best type of control.

Now, this works very well for certain studies in the cancer field, but as you gathered from our presentation today, our present concern and preoccupation in cancer clinical research is with therapy, not so much total metabolic balance studies and the like.

Well, in the big cancer institutions like the one at Sloan-Kettering, much of the research which we want to do and which we support has to be done outside a thing that would fit as a clinical research center. Part of it is radiation. Now, this is——

STATUS OF SLOAN-KETTERING AND MASSACHUSETTS GENERAL HOSPITAL

Mr. Fogarty. Well, Sloan-Kettering certainly would qualify.

Dr. Endicott. Sloan-Kettering is one of the few places where we actually have a center. And this is because they have enough cancer patients requiring hospitalization and precision study in a few areas—chemotherapy—to justify it.

Mr. Fogarty. How about Massachusetts General?

Dr. Endicott. No, sir; we do not have a cancer center there.

Mr. Fogarty. What about a small 40-bed unit that has just been built for terminal cases? It has a laboratory and other good facilities. It was built with the help of Hill-Burton funds.

Dr. Endicott. Massachusetts General Hospital has not applied to us for funds.

Mr. Fogarty. I am not speaking of MGH; I am talking about this other new facility of 40 beds, a couple of year old. It was built for terminal cases. In order to qualify under Hill-Burton, I think they had to add library space to the building.

Dr. **Endicott.** They might qualify.

Mr. **Fogarty.** They are filled up all the time. They have a waiting list all the time.

Dr. **Endicott.** We are still attempting to determine what ought to be done to carry out what we believe to be the intent of the Congress, and certainly what we think is needed for cancer research.

Mr. **Fogarty.** This was started by the Senate, and we went along.

Mr. **Kelly.** It originated in the Jones report. The report of the committee of consultants to the Senate committee was, I think, the first report in which it appeared.

Mr. **Fogarty.** That is right, but all of the testimony that was given was on the other side when this was started. That is why some of us are not as familiar with the qualifications that you have established as we might be.

Dr. **Endicott.** Yes, sir.

STUDY ON FINANCING CLINICAL INVESTIGATION

Well, we have just launched a special study of the problems of financing clinical investigation. We have a task force working—well, the study is being carried out by the Cancer Institute, but personnel who are participating are drawn from a number of operating divisions of the NIH—to try to define what the major problems are and get answers to some very difficult operating problems.

Now, clinical investigation in the cancer field—and this, I think, will hold true in a number of other areas, particularly if they will not fall into the medical specialities but into the surgical specialties, or into psychiatry or into something of this sort.

PROPOSED USE OF RESERVE IF RELEASED

Mr. **Fogarty.** Tell me, Doctor, how you would spend this $11,404,000 that is put aside for forced savings, if these funds were released. You can do that for the record.

Dr. **Endicott.** All right, sir.

Mr. **Fogarty.** And also tell what you are cutting back, if these funds are not released.

Dr. **Endicott.** Yes, sir.

(The requested information follows:)

Administrative Reserve

The National Cancer Institute's 1962 programs have been planned to operate within an allocation of $127,679,000 in 1962. The Institute will not, therefore, find it necessary to reduce ongoing programs to stay within the net appropriation available in 1962. The Institute could not now so late in the fiscal year prudently use the funds in reserve to expand existing programs nor to start new programs.

1962 directed reserves

Research grants	$7,464,000
Training grants	1,275,000
Direct research	256,000
Collaborative studies	2,250,000
Review and approval	144,000
Administration	15,000
Total	11,404,000

FUNDS FOR TRAINING PROGRAMS

Mr. Fogarty. Do you have requests for funds for good training programs that you cannot finance?

Dr. Endicott. Yes, sir; we will have. A number of ours are still pending review at the March council meeting. But we will have some.

Mr. Fogarty. Were all the institutes not required to make a study of this overall problem that we spoke about so much yesterday and today?

Dr. Endicott. Yes, sir. We participated in that study. We were already engaged in one.

Mr. Fogarty. I thought each one made their own recommendations, or sat down and went over the whole program. At least, I was told, over in Baltimore last Wednesday at a heart fund meeting, that the Heart Institute had.

Dr. Endicott. Yes, sir; that is true. There were two or three different things which were done. The very masterful study which was presented for the record this morning by Dr. Shannon, and summarized, was carried out more or less on the basis of a national survey, not so much an internal survey.

But at the same time that was going on, each Institute was asked to study its own training needs and report this to the National Institutes of Health.

Now, these reports were presented late in the fall, and the training funds increased, which were allowed after the administrative reserves were released at that point to activate new training grants this year in the fourth quarter.

Now, I assume—or I am quite sure that we will confer with the NIH again in the preparation of the material which Dr. Shannon is to present in about 2 weeks.

Mr. Fogarty. Dr. Price, what is the situation in this regard; am I right or am I wrong in assuming that the Institutes were all told to sit down and go over this entire program of training and decide how far they should go or what direction they should go?

Dr. Price. You are correct, Mr. Chairman, and on two different counts.

The first thing that we asked the Institutes to do was to take a look at the training objectives in relation to the funds which were available for expenditure in 1962 and to present to the Director a plan for their use which would form the basis for the release of those funds for expenditure in the fourth quarter, as Dr. Endicott has said.

The other was to take a longer range look.

EFFECT OF ADMINISTRATIVE RESERVE ON TRAINING

Mr. Fogarty. Was there any money taken from training by this administrative reserve?

Dr. Endicott. Yes, sir.

Mr. Fogarty. In your report to Dr. Shannon, did your report show that some of this money could have been used in the fourth quarter?

Dr. Endicott. The administrative reserve?

Mr. Fogarty. For training?

Dr. ENDICOTT. For training. Our report to Dr. Shannon was a report as to——

Mr. FOGARTY. I am talking about the matter that Dr. Price was talking to.

Dr. ENDICOTT. Yes, sir. Our report to Dr. Shannon was as to what we felt the training grants and fellowships needs were for this fiscal year.

As a result of this report, the increases which were available—not the administrative reserves, but the increases which remained after the reserve was taken—these funds were released on the basis of our report.

Now, I cannot speak for the other Institutes, but I know in our instance we felt that we had demonstrated a need for additional training funds for new programs which were available in the fourth quarter.

Mr. FOGARTY. All right, how much?

Dr. ENDICOTT. I would have to supply that for the record.

Mr. FOGARTY. Do you have the figure there?

Mr. SEGGEL. No, sir, I do not.

Mr. FOGARTY. All right, you can supply the figure. Go ahead

(The figure of $550,000 was subsequently supplied.)

PURPOSE OF THE MANPOWER TRAINING REPORT

Dr. PRICE. Mr. Chairman, the report to which I was making reference was not directed to what the Institutes would do with this administrative reserve.

Mr. FOGARTY. No, I understand that. I understand it was to review the whole problem and all the problems affecting training programs.

Dr. PRICE. That is correct.

Mr. FOGARTY. And have them review each Institute and give their opinions or their findings to you people at the top level.

Dr. PRICE. Well, Dr. Shannon had pointed out as he presented the manpower study which we had made that the next step was going to be to make use of the information which we had gotten from the Institutes as to what their training objectives for the years ahead may be, and attempt to distill from those estimates some program toward which we might aspire.

The difficulty that we run——

Mr. FOGARTY. If my mail is any indication, Doctor, there is a great demand for these training funds all over the country.

Dr. PRICE. One of the problems that we face in attempting to amalgamate the Institutes' individual projections is that many of them have estimated needs for the same kinds of manpower which are estimated by other Institutes, and we have the problem of trying to decide how much overlap there is in these estimates.

Mr. FOGARTY. That should not be any problem for you to straighten out with all the people you have out there. That would not take long, would it?

Dr. PRICE. Well, we hope that we will have this done within the 2 weeks that Dr. Shannon was referring to.

Mr. FOGARTY. I want to get this figure for 1962, also.

Mr. Seggel. Yes, sir; we are in the process of preparing that, sir. You asked that question yesterday.

Dr. Price. Yes, sir.

SHORTAGES OF TRAINED PEOPLE

Mr. Fogarty. Is there still a shortage of trained people in your area?

Dr. Endicott. Yes, sir.

Perhaps a good example of the kind of problem in the cancer field is the field of radiation therapy, which is one that we have selected as being peculiarly suited to support from the Cancer Institute. This is a specialty which, for all practical purposes, is concerned exclusively with the treatment of cancer patients.

Last year we made a special study. We found that in the United States there were 18 men in training in the field of radiation therapy with 6 completing their training each year. Now, this is not——

Mr. Fogarty. We ought to be ashamed of that record.

Dr. Endicott. Yes, I think we should.

Now, the solution for this problem, though, is a shocker, because there are very few departments equipped to provide adequate training, and we are attempting to get a few in position to do this. And by training I do not mean just training for routine therapy; we are trying, first, to train enough men so that 85 medical schools around the country will have at least 1 man in them who is of an academic research and teaching caliber. This means training him in a radiation therapy department which is doing not just radiation therapy but also research.

Mr. Fogarty. You certainly haven't done much in the way of training radiation therapists.

Dr. Endicott. Well, we made a start. We made a grant which, in order to get the necessary equipment and facilities and resources to accommodate a relatively small number of trainees, was just under $1 million in the first year. And this did not represent the total cost of developing the installation, since a substantial amount of the heavy equipment in it was contributed by industry.

Mr. Fogarty. Where is it?

Dr. Endicott. It is at Stanford. A modern radiation therapy department of a research caliber is a fabulously expensive thing.

So that the thing that will be a nightmare for us in the years to come will be when they look at the operating budget and the number of trainees and derive the obvious conclusion that it costs $50,000 a year to train one man.

Mr. Fogarty. Well, you can always say you told them so. You have established your alibi all right.

EFFECT OF RESERVES ON FUTURE PROGRAMS

All throughout this budget I have noticed places where these cuts, called reserves, made by the Secretary and the Bureau of the Budget, will affect your future programs, and this is another example. You were not even getting the reserve back in 1963. You show an increase of $11,576,000 in 1963 over what the Secretary and the Bureau of the Budget are allowing you to spend this year; but this year you have a reserve of $15,797,000. So in 1963 you still will not be at the level that Congress intended for 1962. Is that right?

Dr. Endicott. That is correct, sir.

Mr. Fogarty. That is not progress, is it?

Some of us had an idea this was going to be Cancer Progress Year. In fact, I got a resolution through the House without much trouble in the closing days of the last session, designating 1962 as Cancer Progress Year. But it has not moved in the Senate yet. I assume it will be reported out, and the President will sign it. But in view of this budget in 1962, perhaps we should change the name of that resolution.

I will not ask you to comment on that. But that is as I see it. I think if you weren't on the record, you would agree with me. I know some of the outside witnesses will agree with that statement. I will make the same statement to them when they come in.

BUDGET FOR FELLOWSHIP AND TRAINING

How much of an increase in 1963 are you going to have for fellowships and training?

Dr. Endicott. For fellowships and training in 1963, we have no increase projected.

FINANCING APPROVED RESEARCH PROJECTS

Mr. Fogarty. As I read the table in front of me, you are going to fall further behind next year than you did in 1962 as far as financing the approved research projects. In 1962 you are going to be unable to finance 224, and in 1963 you are going to be short $8,123,000 to finance 333. Is that figure still firm as far as you are concerned?

Dr. Endicott. Yes, sir. That is the best projection we can give you at the moment.

Mr. Fogarty. But in 1962 you are short 224 and $5,400,000. So instead of catching up with the backlog of applications that you have, you are going the other way. Is that right?

Mr. Seggel. This is the projection of our regular grant program, and it assumes an expenditure for clinical centers at the allocated level in the budget.

Mr. Fogarty. Well, was I not right in the statement I made, if you cannot finance 224 approved projects amounting to over $5 million in 1962, in 1963 you are going to be short for 333 and over $8 million it looks as though you were going downhill; you cannot even keep pace with 1962. That is the thing I cannot understand about this budget; and you think it is a pretty fair budget.

Dr. Endicott. Well, sir, I can do a lot with it.

Mr. Fogarty. Everybody has to give the same answer, I suppose; but you know down deep in your heart you could do a lot more if you had some more money, could you not?

Dr. Endicott. Yes, sir; I believe I could.

Mr. Fogarty. Well, we have in one place what you asked the Bureau of the Budget for and the Department; so I will not waste time in asking about that. But I assume that you asked for much more than the Bureau of the Budget allowed.

Dr. Endicott. It was somewhat larger; yes, sir.

DIAGNOSIS TRAINING

Mr. Fogarty. What is the significance of the apparent discontinuance of the program for technical training in diagnosis and treatment that shows up in the table on page 69?

Dr. Endicott. This reflects a transfer of function and a change in grant form. The item here is training for diagnosis and treatment and the service aspect of this program, by mutual agreement, has been picked up in the cancer control program, where we think it is more appropriate; so that the transfer——

Mr. Fogarty. Where is that in your justifications?

Dr. Endicott. That is under the grants to States and demonstration projects—community demonstration projects and State control programs. These are now being funded through that mechanism, and the program is larger.

Mr. Fogarty. Well you have 121 in 1962. How many are you going to have in 1963 in this area?

Dr. Endicott. Well I can supply it for the record, but as I recall it, it is over 300.

Mr. Fogarty. So you are going ahead in this area?

Dr. Endicott. Yes, sir. This is a very active program.

Mr. Fogarty. All right.

VIRUS RESEARCH ACTIVITIES

Last year in our report we said that we would expect you to strengthen and expand your virus activities. You did mention quite a bit about it in your prepared statement; but is there anything else you want to add?

Dr. Endicott. Yes, sir. I would like to report to you that this is an area where I feel in the next few years we are going to have to develop in this country a new kind of industry to do the types of technical jobs that need to be done here, even to support the research at the National Cancer Institute in Bethesda. We simply cannot accommodate the kinds of equipment and operations which we must have to serve our work right there.

Now in the physical sciences, in the Department of Defense, for example, they reached this stage a long while ago, and as a result of their development needs, research and development needs, a whole series of consulting laboratories, some on a nonprofit basis, some on a profit basis, developed around the country to tackle specific problems, a good many of them in industry.

Now this has not been very common in biology. There are almost no laboratories—there were almost no laboratories of this sort available. They began to develop in response to the chemotherapy program, so we were not starting from scratch.

But it is quite apparent to me that many of the things which need to be done here are not appropriate for universities, and they will certainly not readily be accommodated as a direct operation, and therefore we are going to have to create them elsewhere. We are making a start already.

Mr. Fogarty. By contract?

Dr. Endicott. By contract; yes, sir.

CANCER CHEMOTHERAPY PROGRAM

Mr. FOGARTY. Will this be the same sort of a contract you have for the chemotherapy program?

Dr. ENDICOTT. Much the same; yes, sir.

Mr. FOGARTY. Is that working out all right?

Dr. ENDICOTT. I am very well pleased. I am satisfied it was the only way we could have done as much.

Mr. FOGARTY. You are very well pleased with the way it is going?

Dr. ENDICOTT. Yes, sir.

Mr. FOGARTY. How much of an increase do you have in this year's budget?

Dr. ENDICOTT. There is no increase in this year's budget.

Mr. FOGARTY. Why not?

Dr. ENDICOTT. Well I am not sure; we requested an increase. I am not sure why it is not there.

Mr. FOGARTY. Well we will just blame it on the Bureau of the Budget, then.

CYTOLOGIC EXAMINATION FOR CANCER

Now last year we also urged you and all other appropriate divisions of the Service to do a better job of publicizing the value of a regular cytologic examination for uterine cancer, but I have asked about it two or three times so far during these hearings, and I have not received much information about what you are doing in this area. What have you done?

Dr. ENDICOTT. Yes, sir; we have. It has been rather disappointing to me, though.

The primary approach to the public is, by agreement between the two organizations, undertaken by the American Cancer Society. The National Cancer Institute has concentrated its information efforts in this area in the health professions. Early this year, we approached the American Cancer Society regarding a joint effort of intensive public education, and this was well received by their information people. But the technical advisory committee, made up primarily of physicians, recommended that we not do this. Their belief was that the intensive campaign being carried out by the cancer society in cooperation with the association of women's clubs——

Mr. FOGARTY. National Association of Women's Clubs.

NEED FOR TRAINED PERSONNEL

Dr. ENDICOTT. If we got the response to that that was expected, it would completely saturate our capacity to do "Pap" smears. And the professional group's recommendation was that we would cause more damage by stimulating the public to submit to tests that we could not carry out than if we rode with that campaign this year and reserved the specific campaigns which we had proposed for subsequent years.

So we felt, I felt obliged to accept this recommendation, because it came from the major experts in the field.

Mr. FOGARTY. You say you felt obliged to accept their decision. If you were obliged to accept their recommendations in this area, why do you feel obliged to accept a cut in training?

Dr. ENDICOTT. They are quite different. There is no cut in training of technicians, sir. This is in our budget and is in the process of transfer. I would like to explain that.

Mr. FOGARTY. Well, I would like to know where it shows up, because you show quite a cut in the training program in 1963 compared with the 1962 appropriation.

Dr. ENDICOTT. Yes, there is a specific reduction in this amount.

But about 3 years ago, shortly after the control activity was transferred to the Bureau of State Services—it is still carried in our budget—one of the areas they identified for intensive activity was the training of cytotechnicians, cytodiagnostic technicians, by using demonstration and State grant funds. They put a lot of effort into developing training programs under that support. We have now reached the point where that support is adequate to carry the entire program, and we shall simply drop this item from our training grant budget.

Mr. FOGARTY. You mean to tell me you have enough trained cytotechnicians now to meet the need?

Dr. ENDICOTT. No, sir. But we have as many in training at the present time as we can find good training centers to train. We are attempting to saturate the market here, and to the best of my knowledge, this has been accomplished.

Mr. FOGARTY. You mean you could not train any more of these technicians if you had more funds.

I do not know; but that just does not seem right to me.

Dr. ENDICOTT. My recollection, at the last count, was that there were more than 30 schools training these technicians, and that they were providing funds to pay stipends for all the trainees that they could accommodate. And my impression is—and I think this is correct—that this number of training centers represents what is available of the standard that the Bureau of State Services would wish to support.

Perhaps Dr. Terry has additional comments.

Dr. TERRY. No; I just wanted to know whether you understood how many were in training at the present time.

Mr. FOGARTY. Well, I think more could be in training. That is just my offhand opinion. You may not agree with it. I think you could find places in this country where you could train more personnel.

APPROPRIATION STRUCTURE

The way this is set up in the budget doesn't make it any easier to get at. It seems kind of mixed up to me. Here this appropriation is carried in your Institute, and it is under the administration of the Bureau of State Services; is that right?

Dr. ENDICOTT. I am very happy with this arrangement. I think it is working very effectively.

Mr. FOGARTY. But they administer the program and should be the ones to justify the budget. It seems to me to just complicate things to have one bureau running a program and another bureau defending the request for funds. Why do you not transfer it over to the Bureau of State Services budget?

Mr. KELLY. Mr. Chairman, if the committee would like it done that way and does not include it in the bill, we would like to have that in the report. Now, you did put it in the report in connection with the dental resources program. And we did make the transfer to the Bureau of State Services. We knew that there were several other aspects of our budget that had a degree of comparability with this.

Mr. FOGARTY. Why do you not get me up a list?

Mr. KELLY. All right, sir.

Mr. FOGARTY. I will take a look at it.

Mr. KELLY. We were concerned if we did that, the Congress would feel that we had split programs like cancer and mental health and heart into multiple places in our budget and that you wanted it all together in one place so you could talk to it and could consider it in one place.

RADIOTHERAPY PROGRAM

Mr. FOGARTY. Now, you have a radiotherapy program you say is being developed. Is this a new program in 1962?

Dr. ENDICOTT. This we identified as a special area of emphasis last year, and early this fiscal year we brought on a senior person on loan, really, from Columbia University to devote full time to the development of research grants training and center program in the radiation area, Dr. Nora Tapley, from the radiation department at Columbia. So that it is a new program, really, this year. And it is moving along quite well. We have a few active grants already, and I think there are roughly 12, a dozen, applications pending for review at the March Council meeting.

These are, as you would suspect, rather large grants. I do not know how many will be approved.

GHANA RESEARCH CENTER

Mr. FOGARTY. Was the Institute's research unit in Ghana, Africa, put there for medical reasons or for political reasons?

Dr. ENDICOTT. It was put there for medical reasons, sir. Last spring, the Director of the newly created National Institute of Health and Medical Research in Ghana visited the United States and approached us at the National Institutes of Health with the proposal that, if we would send a group of first-rate scientists out there to work, they would provide the resources to construct laboratory buildings and provide appropriate housing for the staff members of NIH. Shortly after this visit, President Kennedy received an invitation from the President of Ghana to enter into such a collaborative program, and during the summer Dr. Cummings and I went to Ghana, at Dr. Shannon's request, to evaluate the research potentialities there. We returned and recommended to Dr. Shannon that we felt there were excellent research opportunities, almost unique research opportunities there. We recommended that such a laboratory be established.

Now, I must confess I did not know that I would be stuck with doing it. But at any rate, I made that recommendation.

Subsequently, the decision was made to go ahead with it, and for purposes of administration it was placed in the Cancer Institute. Now, we are providing the management function of this laboratory for NIH. The research which will be done there will probably be mostly in the fields of parasitic diseases and infectious diseases and nutritional diseases, at least in the early years. But we are administering it, in effect, for all of NIH.

SWEDISH CANCER RESEARCH

Mr. Fogarty. How are you doing in Sweden? Dr. Bjorklund is coming over here pretty soon; is he not?

Dr. Endicott. Yes, sir. He is scheduled to be in the United States in the next few weeks, I believe. He has had some publicity to which you probably are referring. There has been a dispute in Sweden as to whether he should or should not at this point proceed with a program in which he is attempting to evaluate the immunizing potentiality of certain preparations derived from human cancer cells. There is honest, substantial difference of opinion as to whether he should go ahead or he should not. I believe it is the Swedish Academy of Medicine—I am not sure, but I believe that is the right organization—which in effect has made a public statement that this work should not proceed.

Mr. Fogarty. The paper says:

> Dr. Arthur Engel, head of the Royal Medical Board, disclosed today that he had tried in vain to persuade Dr. Bertil Bjorklund to postpone his current cancer vaccine tests.

But he went ahead on television, and inoculated himself?

Is it so that he and his staff of 14 received the bulk of their funds from the National Cancer Institute?

Dr. Endicott. At the present time I believe that is true; yes, sir.

Mr. Fogarty. You sent someone over there; did you not?

Dr. Endicott. Yes. We have had investigators over there and he has been in our laboratories before.

Mr. Fogarty. What did they go over for; what did they report to you?

Dr. Endicott. Dr. Bjorklund is regarded quite highly as an investigator in the cancer field. This is not to say that everyone approves of every project he undertakes; but I would say—I think you would agree, Dr. Mider—that he enjoys a good reputation.

Mr. Fogarty. Is he a young man?

Dr. Endicott. What is his age?

Dr. Mider. I would guess he is in his early forties.

NATURE OF GRANT TO DR. BJORKLUND

Mr. Fogarty. What is this, a 5-year grant he has?

Dr. Endicott. I am not sure at what stage it is at the moment, but he has been supported for some little time. The number on the grant may be as high as C–7 or 8.

But I think his current commitment that we have to him is over a 5-year period, and he is somewhere near midstream in it.

Mr. Fogarty. Where is he doing this work?

Dr. Endicott. I am not too sure just where it is being done, sir.

Mr. Fogarty. Will you put that in the record?

Dr. Endicott. Yes, sir.

(The requested information follows:)

(The work of Dr. Bjorklund is being done at the Immunological Research Laboratory, Stockholm, Sweden.)

Mr. Fogarty. Were these people you sent over there impressed with his work?

Dr. Endicott. They were, yes. As a matter of fact, there has been active interest in the part of members of our intramural staff, recommending to me that we increase his support; that he is rather highly thought of.

Perhaps Dr. Mider would like to comment. I think he knows him.

Dr. Mider. Some years ago, Mr. Chairman, Dr. Bjorklund described material from human blood which killed human cancer cells growing in tissue culture. At about the same time, Dr. Maurice Landy, of the National Cancer Institute's staff, came up with a similar material. It did not work on human cancer cells but worked on animal cancer cells. Dr. Bjorklund and Dr. Landy worked together for a few months.

Mr. Fogarty. How do you spell that?

Dr. Mider. Landy, L-a-n-d-y. He is on our staff.

It seemed very important to find out whether they were dealing with the same thing or whether they were two different things. So they got together and proved they are dealing with two entirely different principles. Dr. Landy has maintained some contact with Dr. Bjorklund's research and Dr. Bjorklund is well aware of what Dr. Landy is doing.

When I was in the Cancer Institute, there was some discussion of the potential for a vaccine. I do not think that that was a major concern of Dr. Bjorklund at that time.

Dr. Endicott. No.

Dr. Mider. But logical extensions of his research through its development might make it desirable to produce some type of prototype vaccine. I do not think we are completely aware of that phase of his efforts. We do not know as much about that as the substance in blood.

NILES, ILL., LEUKEMIA OUTBREAK

Mr. Fogarty. Tell me a little bit more about this outbreak of leukemia in Niles, Ill. You mentioned it in your prepared statement in connection with some drug that you are excited about.

Dr. Endicott. This was brought to our attention some months ago. A group of epidemiologists from the Communicable Disease Center and from the Cancer Institute went to Niles and looked into the situation and followed it rather closely ever since. This is a suburb of Chicago.

The cases have occurred among children in one of the parochial schools. In a relatively short time, some seven cases of acute leukemia appeared in this school population.

Now, this is way beyond the incidence that you would expect in a population group of that size in that period of time. It may be chance, because this sort of thing does happen by chance. But it seems abnormally high. Because of our preoccupation these days with the possibility of viral etiology of acute leukemia, this then becomes a very attractive research situation in order to determine whether the setting was right, and the facts would fit with the concept that the disease here was of viral origin, and that the disease spread from child to child in the school.

Now, if I may go off the record for a moment, because this is not published yet?

Mr. FOGARTY. All right.

(Discussion off the record.)

Mr. FOGARTY. All right, back on the record.

Is there anything else you want to say?

Mr. ENDICOTT. No, sir.

Mr. FOGARTY. Dr. Mider?

Dr. MIDER. No, sir.

Mr. FOGARTY. Does anybody else want to say anything?

Very well, then. We shall convene at 10 o'clock tomorrow morning.

(The following additional material was submitted at the request of the committee:)

MORTALITY, MORBIDITY, AND COST OF CANCER

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, PUBLIC HEALTH SERVICE, NATIONAL CANCER INSTITUTE

Statistics of the annual number of deaths and total current number of disabilities caused by the major diseases dealt with in the National Cancer Institute, and the estimated annual cost to the Nation.

I. Cancer deaths in 1960 (unpublished data supplied by the National Office of Vital Statistics Division):

Buccal cavity and pharynx	6, 330
Digestive system	90, 350
Respiratory	39, 380
Breast	23, 650
Genital organs	38, 840
Urinary organs	12, 700
Other sites	28, 610
Leukemia	12, 290
Lymphomas	13, 110
Total, all sites	265, 260

II. Cancer disability in 1960 (estimated on the basis of data supplied by the National Cancer Institute and the National Health Survey Division):

(*a*) Estimated cases under treatment	782, 000
(*b*) Estimated person-days of disability (these estimates have a large margin of error):	
1. Restricted activity	38, 800, 000
2. Sick in bed	23, 900, 000

III. Cancer's cost to the Nation in 1960:

(*a*) Hospital bill—$350 million (estimated by the American Cancer Society).

(*b*) Loss of income—$91 million (estimated by assuming that 1 in 7 person-days of restricted activity represents a lost working day, that there are 250 working days in a year, and that an average annual income is $4,200). This must be considered a minimal estimate. Not included in this estimate is the loss of productivity due to retirement for cancer disability nor the loss of potential productivity because of a cancer death during the working years.

(*c*) Estimates based on the average annual contribution per member of the labor force (age 18–65) to the gross national product indicate that cancer brings about a loss to society in goods and services valued at approximately $15 billion per year.

HIGHLIGHTS OF PROGRESS IN RESEARCH ON CANCER 1961

PART 1. SELECTED HIGHLIGHTS OF RESEARCH ACCOMPLISHMENTS AND PROGRAM DEVELOPMENTS [1]

VIRUS RESEARCH

Viruslike particles seen forming in pancreas cells of normal chicks and embryos

One of the ways of obtaining a better understanding of virus-host relationships is to learn where and how viruslike particles multiply within hosts showing no evidence of malignant disease.

This approach has been used by Dr. Robert F. Zeigel, laboratory of viral oncology, in an electron microscope study designed to produce information about the site and mode of production of viruslike particles found in tissue from healthy fowl.

Dr. Zeigel observed viruslike particles being formed by "budding" from the walls of pancreas cells of normal chicks and embryos. When budding particles were found in the pancreas, mature particles were visible in other tissues. When no particles were seen in the pancreas, none were found elsewhere.

That the particles actually were viruses has not been established, but they were similar in structure to the fowl tumor viruses. The latter are widely distributed, and are present even in apparently healthy colonies.

The observation of particles in the embryos was interesting from another standpoint; it supported the belief that virus can be transmitted from mother to offspring in the egg. (Journal of the National Cancer Institute 26: 1011–1039 (1961).)

Specially designed chemical compounds inactivated viruses

Results of research by scientists in the Laboratory of Chemical Pharmacology have shown that specially-made chemicals can inactivate viruses that ordinarily attack bacteria. According to a report given by Dr. Peter Mora at the 18th International Congress of Pure and Applied Chemistry in Montreal in August, viruses permanently lost their ability to infect bacteria as a result of treatment under suitable conditions with compounds having strong, negative electrical charges. The compounds were polysaccharide molecules to which sulfate groups were linked chemically

Bacterial viruses (bacteriophages) are tadpole-shaped organisms whose head and tail are made of protein. Packed tightly inside the head is deoxyribonucleic acid (DNA), the infective portion of the viruses.

The negatively charged compounds used in this work appeared to act by drawing certain positively charged compounds (amines) away from the viral DNA. The remaining negatively charged components of DNA repelled one another, thus expanding the tightly coiled DNA molecules inside the head of the viruses. As a result, DNA could not pass through the tail and into the bacterial cell wall.

These findings are being followed up to determine whether the polyoma virus. which induces tumors in animals, can be inactivated in the same way.

NCI scientists study lung tumors induced by polyoma virus

The increasing prevalence of human carcinoma of the lung has highlighted the urgent need for studying the disease in the laboratory. An important step is the production of lung tumors in laboratory animals, and a number of reports have appeared in the scientific literature on the methods—particularly the use of hydrocarbons—that will induce such tumors in mice, rats, and rabbits. The Syrian hamster appears to be a suitable animal for the study of lung carcinogenesis, because spontaneous lung tumors have not been observed in this species and pulmonary infections are rare.

About 2 years ago, Dr. Bernice Eddy, Laboratory of Virology and Rickettsiology, Division of Biologics Standards, and Dr. Sarah E. Stewart, Laboratory of Viral Oncology, National Cancer Institute, reported that subcutaneous inoculation of polyoma virus induced undifferentiated lung tumors in newborn hamsters. This observation provided an opportunity to investigate the possible viral etiology of lung cancer, and was the basis for the present study by Dr. Alan Rabson, of the National Cancer Institute's Pathologic Anatomy Branch, and his associates in the Laboratory of Pathology of the effect of intratracheal inoculation of the virus in hamsters.

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[1] The items presented in this report are representative of work conducted and supported by the National Cancer Institute. Institute staff scientists are identified by the laboratory or branch with which they are connected and grantees by their institution. Most of the results were reported by groups of investigators, but for the sake of brevity, only the senior author is identified in most of the summaries.

Of 22 weanling (26 to 38 days old) animals inoculated, 16 died by the 400th day. Lung tumors with histologic features of bronchiolar carcinoma, alveolar-cell carcinoma, and squamous-cell carcinoma were found in six hamsters that died 164 to 391 days after inoculation. Of the 10 animals in which no tumors were seen, 5 that died 27 to 195 days after inoculation were found to have proliferative lesions of bronchiolar and aleveolar-lining cells. One of the tumors has been transplanted, and has retained its squamous differentiation through four generations.

An attempt was made to demonstrate the presence of free virus by adding a suspension of one of the lung tumors to tissue cultures of milk-adapted P388 D_1 cells. However, no evidence of a cytopathic effect was observed.

Further work is in progress to investigate the role of the polyoma virus in the production of these tumors. (Journal of the National Cancer Institute 25: 937–965 (1960).)

New technique insures recovery of Rous virus from turkey tumors

Drs. Victor V. Bergs and Vincent Groupé, Rutgers University, New Brunswick, N.J., have reported a way of recovering some virus from virus-induced turkey tumors that often yield none when conventional methods are used. Their technique may be helpful in efforts to recover viruses from human and other cancers.

The rationale for the technique is that the presence of antibody in the blood and other body fluids of a tumor-bearing host neutralizes the virus and prevents its recovery from tumors induced by Rous sarcoma virus. Recovery is particularly difficult from tumors induced by a small dose of virus.

Drs. Bergs and Groupé have now reported that when such tumors were grown for several weeks in antibody-free tissue cultures, virus could be recovered from the culture fluid. The amount of virus recoverable depended on the size of the dose used to induce the tumors.

The procedure used in starting the cultures consisted of washing the tumor tissue three times with salt solution, mixing it for an hour with trypsin to separate the tumor cells, then washing the cell suspension three times with salt solution before placing it into the culture medium. (Science 134: 192 (1961).)

Tumor-inducing nucleic acid is isolated from rabbit papillomas and papilloma virus

Tumor-inducing nucleic acid has been isolated from papillomas in cottontail and domestic rabbits and from papilloma virus by Drs. Yohei Ito and Charles A. Evans at the University of Washington in Seattle. This finding indicates that a tumor-inducing factor is present even when little or no virus can be found in some virus-induced tumors.

The domestic rabbit papilloma is one such tumor. The cottontail papilloma, on the other hand, ordinarily is a rich source of the virus (as demonstrated initially in 1933 by Dr. Richard E. Shope).

The material used in the present work contained nucleic acid isolated when papillomatous tissue or papilloma virus was treated with phenol to remove protein. Nucleic acid derived from both tissue and virus induced papillomas when assayed in domestic rabbits.

The nucleic acid obtained from papillomas of domestic rabbits (which appeared to contain no virus when tested by conventional methods) proved less potent than that from cottontail tumors.

Treatment with rabbit serum that contained neutralizing antibodies to the papilloma virus did not diminish the tumor-inducing activity of either the cottontail or the viral nucleic acids, suggesting that intact virus was absent. The cottontail nucleic acid was shown to be deoxyribonucleic acid (DNA) rather than ribonucleic acid (RNA).

These findings indicate that virus may be present in an altered form, that is, nucleic acid without the protein coat, in domestic rabbit papillomas, which is consistent with the failure to find virus in such tumors.

This work adds the papilloma virus to a long list of plant and animal viruses from which infective nucleic acids have been isolated by phenol extraction. The previously isolated viral nucleic acids have generally been found to be less potent than whole virus. The present report does not provide information on the relative potency of the nucleic acid from papilloma virus. (Journal of Experimental Medicine 114: 485–500 (1961) and Virology 12: 596–601 (1960).)

Virology Research Resources Branch program assists investigators

The National Cancer Institute's continuing interest in research on the relationship of viruses to cancer—particularly cancer in man—was demonstrated during the past year by the establishment of a Virology Research Resources Branch whose activities stimulate and service virus-cancer research throughout the country.

The Virology Research Resources Branch, headed by Dr. Harvey I. Scudder, is under the direction of Dr. Stuart M. Sessoms, National Cancer Institute, Associate Director for Collaborative Research. The Branch's program is concerned with making available virus-cancer research materials and services which have been in short supply. These include highly characterized mammalian cell lines for tissue culture work, normal and malignant human tissue, viral identification reagents, and virus-defined laboratory animals.

The first mammalian cell lines to be characterized and certified under the auspices of this program are now ready for deposit in the cell bank operated by the American Type Culture Collection. These seed stocks will be distributed to qualified investigators on request. Viral identification reagents produced under contract are already in distribution. Work is underway on the development of a virus-defined mouse as well as techniques and facilities to insure the efficient utilization of this animal.

A new facet of the program administered by the Virology Research Branch is its encouragement of research on antiviral prophylaxis and therapeutics, with inquiry into the basic problems of viral pathogenesis in relation to the host response to both viral infection and viral neoplasia.

The program plans to direct considerable effort toward development of a suitable virus-defined primate for cancer etiology studies. In addition, the staff has initiated certain information services for investigators in the cancer-virus field and is concerned with the problems of training across the many disciplines represented.

As of December 15, 1961, 6 contracts, totaling $964,613, had been awarded for the development and production of items needed for virus-cancer research.

CARCINOGENESIS

Carcinogenic hydrocarbons shown to accumulate in cytoplasm of cells

A helpful step in efforts to understand how an agent acts to cause cancer is to learn how the agent enters a living cell and where it accumulates within the cell. Data of this kind about cancer-causing (in animals) hydrocarbons have been obtained in a collaborative study by Dr. Kenneth M. Richter, University of Oklahoma Medical Center, and Dr. Virender K. Saini, Dalhousie University, Halifax, Nova Scotia.

The behavior of three compounds, dibenzanthracene, benzpyrene, and methylcholanthrene, was studied in tissue cultures of mouse testicular cells; blood cells (red and white cells and platelets) of man, mouse, and fowl; chick heart, rat sarcoma, and HeLa (human cervical carcinoma) cells. Ultraviolet light, in which hydrocarbons fluoresce, was used to locate the compounds in cells examined through the microscope.

Hydrocarbons were visible in this way in all the cell types studied except the red blood cells.

These compounds appeared to accumulate substantially in the cytoplasm, particularly in the Golgi bodies of cells having this apparatus and in the granular components of other cells. Each cell type studied showed a characteristic distribution.

Hydrocarbons were not detected in any part of a cell nucleus, except the membrane surrounding the nucleus. Various amounts of the compounds were found in some of the metabolic products formed by the cells.

The study also confirmed reports of other investigators that crystals of hydrocarbons are soluble in body fluids, and therefore can enter cells without being carried in special solvents.

The investigators conclude that fundamental differences in the composition, structure, and physiology of cells appear to influence the observed behavior of the hydrocarbons. (The American Journal of Anatomy 107: 206–235 (1960).)

Derivative of bile acid appears to cause sarcomas in some laboratory mice

The possibility that some of man's natural body products can cause cancer is an area of continuing interest. Some such products, including the sex hormones and the acid components of liver bile, are similar in chemical structure to substances capable of inducing cancer in animals, such as the hydrocarbon, 20-methylcholanthrene. Furthermore, the latter compound can be derived chemically from either of the two principal bile acids, cholic desoxycholic acids. However, attempts to induce cancer in animals by injecting these acids have not produced consistent results.

Drs. A. Lacassagne, N. P. Buu-Hoi, and F. Zajdela, of the Radium Institute, University of Paris, France, have now reported that apocholic acid, a derivative of cholic acid, appears to have a definite cancer-causing effect on mice.

In this study, 42 3-month-old inbred mice each received 10 injections, at 10-day intervals, of apocholic acid dissolved in olive oil. Within 217 days after the first injection, 14 mice died without tumors at the site of injection. The first tumor observed, a sarcoma, appeared 240 days after the first injection. Sarcomas later developed in three other mice. Mice that were untreated or that received injections of olive oil alone did not develop such tumors.

These findings reemphasize the need to determine whether natural products are converted to cancer-causing forms in the course of man's normal metabolism. (Nature 190: 1007–1008 (1961).)

FIELD STUDIES AND DIAGNOSTIC RESEARCH

Simplified cell collection technique may extend use of gastric exfoliative cytology

Exfoliative cytology, although proven accurate for differentiating benign from malignant gastric lesions, is not widely used for diagnosis because of complex cell collection techniques and the shortage of trained personnel. Drs. Lloyd L. Brandborg, Lilian Taniguchi, and Cyrus E. Rubin, of the University of Washington School of Medicine, Seattle, evaluated test results of a simple and rapid chymotrypsin lavage technique for collecting exfoliated gastric cells.

The new technique was tested on patients previously diagnosed with reasonable certainty as possessing a benign or malignant gastric lesion. Comparisons were made with an older chymotrypsin technique employed in their laboratory and with techniques such as balloon abrasion and saline lavage reported in the literature.

With the new technique, it was possible to diagnose 92 percent of the cancerous lesions and all benign lesions correctly in an hour. With the older technique, 89 percent of the cancerous lesions and 98.6 percent of the benign lesions were diagnosed in approximately 3 hours.

These results show that there was no loss of diagnostic accuracy despite the fact that all of the specimens in the short-method series were collected by an 18-year-old high school graduate after only a few days' instruction. In contrast, experienced technicians collected for the longer method. Furthermore, more than 80 percent of the slides obtained by the short method were rated easy to read by experienced cytologists. Only 68 percent of the long-method slides and 40 percent of the slides obtained by other techniques were so rated. It appears, therefore, that the short-method is suitable as a routine laboratory procedure.

The investigators conclude that the results warrant further study to determine whether selective collections for screening of large numbers of asymptomatic individuals is practical in small laboratories not possessing highly trained personnel. If so, malignant gastric lesions might be detected at an early, potentially curable stage. (Cancer 14: 1074–1080 (1961).)

Institute field studies carried out in many geographic areas

The emergence of field studies as a major approach to the problem of cancer has resulted in the regrouping of investigations in the area under a single associate director. Many new projects have been initiated during the past year in order to obtain more information about significant genetic, environmental, and cultural factors responsible for cancer. These projects are being carried out through direct operations at the Institute itself or in other geographic areas, or through contracts with universities or research institutes.

Studies of the biometry and epidemiology branches are particularly concerned with identifying and analyzing genetic and environmental factors responsible for cancer in selected population groups. For example, scientists of the epidemiology branch are investigating an unusual pattern of cancer incidence observed in Washington County, Md., to determine whether it may be related to environmental variables such as ionizing radiation and soil chemicals. The epizoology section of this branch, centered at Michigan State University, has begun a series of studies to determine the relationship between cancers occurring naturally in animals and those occurring in man. In another study, questionnaire data have been collected on a large number of leukemic and normal children at 12 medical centers. Analysis of these data, now underway, may reveal important new information about pre- and post-natal factors which may predispose to childhood leukemia.

The carcinogenesis branch is emphasizing the study of chemical carcinogens in the environment. A number of compounds are under intense investigation to learn the precise biochemical reactions involved in the production of malignancy.

The possibility of diagnosing cancer before the appearance of symptoms has been amply documented by the results of the vaginal cytology program. A recent finding by investigators of the diagnostic research branch involved development of a technique by which a chemical activity may be measured to indicate malignancy. In other histochemical, diagnostic investigations, certain reagents which are useful for differentiating between true leukemias and leukemia-like reactions have been developed. These findings may have important implications for the early diagnosis of cancer.

CHEMOTHERAPY AND OTHER CLINICAL RESEARCH

Combination of drugs effective treatment for cancer of testis

Encouraging results in treating metastatic cancer of the testis with drugs have been reported by Dr. Min C. Li and his associates at the Memorial Sloan-Kettering Cancer Center, New York City.

Their study was an extension of research on tumors of embryonic origin begun when Dr. Li was a member of the staff of the National Cancer Institute's endocrinology branch. At that time, he and his colleagues reported that choriocarcinoma of the uterus, arising in women during or after pregnancy, was susceptible to treatment with methotrexate. The male tumors, such as seminoma, embryonal carcinoma, or choriocarcinoma, or mixtures of these histological types, did not respond to methotrexate or 6-diazo-5-oxo-L-norleucine.

The present study was undertaken to evalaute in 36 male patients the effect of therapy with combinations of 3 different classes of drugs. In the patients with testicular choriocarcinoma, the amount of the hormone, chorionic gonadotropin, produced by the tumor and excreted in the urine, provided a quantitative measure of response to therapy. Other objective evidence was obtained by chest X-rays, intravenous urograms, and measurement of palpable or visible tumor masses.

A combination of three well-known drugs—methotrexate (an antimetabolite), chlorambucil (an alkylating agent or cell poison), and actinomycin D (an antibotic)—was the most effective regimen. Seven of the 23 patients treated with this combination showed virtually complete disappearance of pulmonary metastases and palpable masses, or both; at the time the report was prepared, three of the seven had continued in good health for 9 to 18 months. An additional 5 of the 23 patients showed partial regression of metastases for 1 to 4 months.

Tumor regression was associated with a fall of urinary chorionic gonadotropin in patients with choriocarcinoma. All the combinations tested produced substantial, but reversible, hematological, gastronintestinal, and dermatological side effects. (Journal of the American Medical Association 174: 1291–1299 (1960).)

Treatment of advanced cancer of adrenal cortex by o,p'–DDD described

Scientists of the endocrinology branch have reported the latest results obtained in a continuing clinical study of the chemotherapy of advanced adrenocortical carcinoma. The study is of particular interest scientifically because (1) the drug (o,p'–DDD) used acts specifically upon one type of tissue and also upon a neoplasm arising from that tissue; (2) the tumor produces an excessive amount of hormone in the urine; hence, the quantity of hormone provides a means of measuring the progress of treatment; (3) spontaneous remissions in this disease are unknown, so that any remissions observed may be attributed to the drug treatment.

The study originated in an observation by Nelson and Woodward in 1949 that feeding dogs DDD, an insecticide, resulted in damage to the adrenal cortex. Nichols in 1957 and Cueto in 1958 found that the agent responsible for the adrenocorticolytic effect was the ortho, para prime isomer (o,p'–DDD), which occurs as a contaminant in commercial DDD. The first study of treatment of adrenocortical cancer patients with o,p'–DDD was made by scientists of the endocrinology branch, and their initial observations were reported in 1959.

The present report summarizes the response of 18 patients treated at the Clinical Center over a 2-year period. The average course of treatment was 8 to 10 grams of o,p'–DDD daily, given orally for 4 to 8 weeks. The drug was furnished by the Edcan Chemical Co., Norwalk, Conn., for research purposes.

Response to treatment was measured by regression of metastases (that is, decrease in size of pulmonary or abdominal metastases) and by sustained decrease, to less than 70 percent of initial levels, in steroid excretion.

Objective regression of metastases was observed in seven patients; significant steroid suppression only, in seven additional patients; and no apparent effect in four.

No evidence of toxicity was observed in the liver, kidneys, or bone marrow. All patients experienced significant loss of appetite and nausea, and some showed central nervous depression varying from mild lethargy to somnolence. These toxic effects were reversible. High doses of the drug caused histologic damage and functional impairment of the normal adrenal gland.

The late Dr. Delbert M. Bergenstal was the senior author of the report. Coauthors were Drs. Roy Hertz, Mortimer B. Lipsett, and Richard M. Moy. (Annals of Internal Medicine 53: 672–682 (1960).)

Drug treatment restores health to patients with advanced choriocarcinoma

Dr. Roy Hertz and his associates of the endocrinology branch have reported the results of 5 years' experience in using drugs to treat women with choriocarcinoma, a rare form of cancer that arises from embryonal cells in the womb of pregnant women.

Since 1955, a total of 63 women admitted to the Clinical Center have received intensive courses of methotrexate; 14 were also given brief courses of vinblastine after developing resistance to methotrexate.

The disease had spread, in all the patients, from the uterus to other parts of the body, most frequently to the lungs before therapy was begun. When choriocarcinoma is so far advanced, spontaneous regression rarely occurs.

Changes in the amount of the hormone, chorionic gonadotropin, produced by the tumor and excreted in the urine, provided an index of response to the drugs. Changes in the radiological appearance and size of tumors were also used to evaluate response.

At the time the report was prepared, 30 of the patients were free from evidence of disease. A few showed no sign of recurrence for more than 5 years after treatment was completed. They are the first patients with widespread cancer whose health has been restored for as long as 5 years following chemotherapy. (Proceedings of the American Association for Cancer Research 3: 235 (1961).)

Results of clinical trial of uracil mustard report

The results of a clinical trial of uracil mustard, an alkylating agent that was given orally to patients with lymphomas (Hodgkin's disease and lymphoblastoma) and chronic lymphatic leukemia, have been reported by Drs. B. J. Kennedy and Athanasios Theologides, University of Minnesota Medical Center, Minneapolis.

Synthesis of uracil mustard, 5-bis-(2-chloroethyl)-aminouracil, was reported in 1958 by Drs. Douglas A. Lyttle and Harold G. Petering of the Upjohn Co., Kalamazoo, Mich. They and other investigators, including National Cancer Institute scientists Drs. Montague Lane (now with the M. D. Anderson Hospital, Houston, Tex.) and Margaret G. Kelly, showed that the compound was active against a number of tumors in rats and mice. The Upjohn Co. provided the drug for research purposes.

Large doses of the drug, 0.5 to 0.8 mg. per kilogram of body weight over 3 days, were given to patients initially in the present study, and repeated when necessary to treat recurrence or to maintain improvement, until resistance to the drug developed.

The criteria for judging objective response included a significant decrease in size of enlarged lymph nodes and tumor masses; reduction in size of the spleen; disappearance of fever; lowering of elevated white blood cell count to normal levels, with an increase in hemoglobin, in leukemia patients; and healing of leukemic ulcers.

Objective improvement for periods ranging from less than 3 to more than 12 months occurred in 15 of 19 patients with chronic lymphatic leukemia and in 16 of 27 with lymphomas, but not in one each with subacute lymphatic leukemia, Kaposi's sarcoma, and severe mycosis fungoides.

Side effects of the therapy were relatively mild. Loss of appetite, nausea, and vomiting were seen in some patients on days that uracil mustard was given, but were less intense than the gastrointestinal symptoms produced by nitrogen mustard, which is a standard chemotherapeutic agent for lymphomas and chronic leukemia. The two drugs are chemically related, but the latter can be given only intravenously. Other side effects seen in some patients were depression of the number of circulating white blood cells for brief periods and more prolonged decreases in platelet levels.

The authors concluded that the therapeutic benefits of uracil mustard given orally were similar to those of other mustard compounds. They recommended further studies to determine the relative merits of various dosage schedules and to compare the effects of uracil mustard to those of nitrogen mustard. (The New England Journal of Medicine 264: 790–793 (1961).)

New compounds designed to combine anticancer activity of two agents

Several new compounds designed to combine the anticancer activity of antimetabalites and alkylating agents have been synthesized by Robert C. Elderfield and R. Stanley McElhinney at the University of Michigan.

Each compound contains an alkylating group and an amino acid, slightly altered so that it blocks cell growth and reproduction. One of the compounds is particularly interesting because it contains aspartic acid, an amino acid which other investigations have shown is present in significantly lower amounts in mouse tumors than in normal tissue.

The compounds synthesized in this work are now being screened for anticancer activity in animals under the research program of the Cancer Chemotherapy National Service Center.

Work of a similar nature was reported last year in a lecture at the National Institutes of Health by Prof. L. F. Larionov, head of the Institute of Experimental and Clinical Oncology in Moscow. Professor Larionov reported on synthesis of so-called alkylating metabolites and the promising results obtained in testing them against animal tumors.

This rational approach hopefully will lead to development of drugs that will attack cancerous tissue without damaging normal tissue. (The Journal of Organic Chemistry 26: 1917–1923 (1961).)

Combination of techniques used in treating patients

Regional drug perfusion previously has been shown to be beneficial therapy for some forms of cancer. Since the major blood vessels in the perfused area are isolated from those in the rest of the body, drugs can be given in large doses that would be unsafe for systemic use because of undesirable side effects. Other laboratory and clinical studies have indicated that warming enhances the antitumor effects of alkylating agents, and that cooling the body protects bone marrow (a frequent site of damage), possibly by reducing the rate of blood flow in cooled tissue.

Drs. William W. Shingleton, Roy T. Parker, and Stephen Mahaley have been combining these techniques in treating cancer patients at the Duke University Medical Center, Durham, N.C. According to the present report, blood containing an alkylating agent was heated so that it raised the temperature of the perfused area by 1° to 2° centigrade. At the same time, the rest of the body was cooled by 5° to 6°.

These procedures were used for abdominal or pelvic perfusion in treating 25 patients with such forms of cancer as carcinoma of the colon, uterine cervix, ovary, rectum, and pancreas. The drugs used (all singly) were A–139, cyclophosphamide, L-phenylalanine mustard, and nitrogen mustard.

At the time the report was prepared, 9 patients were alive for periods ranging from 2 to 14 months after treatment; the other 16 were dead of progressive disease. In 9 of the 25 patients, significant bone-marrow damage was observed. However, no deaths could be attributed directly to this effect, or to the surgery involved in isolating the tumor-bearing area.

The authors emphasize that they have treated too few patients whose diseases were comparable in type and extent to determine how these procedures affect survival. (Surgery, 50: 260–265 (1961).)

Dermatologists study effects of methotrexate on basal-cell carminoma

Dr. Eugene J. Van Scott and his associates in the dermatology branch have reported previously that methotrexate inhibits mitosis in the roots of growing scalp hairs. This evidence of drug-induced damage to tissues derived from the epidermis provided the rationale for a study of the effects of methotrexate on basal-cell carcinoma.

The drug was given to seven patients with tumors so extensive they could not be treated successfully by surgery or radiation. Most tumors became smaller, and a few disappeared, but the responses were temporary and were accompanied by toxic side effects. In all patients, tumors that were inflamed prior to therapy showed the best response.

These observations have suggested that therapy with methotrexate may be enhanced by exposing tissues to small doses of radiation in order to provoke inflammation and accelerate mitosis. Studies of such a procedure are underway. (American Medical Association Archives of Dermatology, 82: 762–771 (1960).)

Studies show distant metastases in patients with head and neck cancer

Current concepts indicate that head and neck cancers rarely metastasize below the clavicle. Scientists of the Surgery Branch have reported studies which indicate that distant metastases do occur in patients with this type of malignancy.

The studies now reported by Drs. Marvin S. Arons (now with Georgetown University Hospital) and Robert R. Smith were conducted on 89 patients admitted to the clinical center over a period of 7 years. The patients were diagnosed as having extensive epidermoid carcinoma except for two with adenocarcinoma of the paranasal sinuses. The following period was 6 to 76 months. Admission X-rays revealed no evidence of pulmonary or skeletal metastases.

Distant metastases developed within 2 years in 23 percent of 72 patients treated by defintive surgery. Local recurrence developed within 3 years in 47 percent.

In the majority of the patients, the distant metastases were confined to the lungs. Thus, the study emphasizes the importance of routine chest X–ray as a postoperative followup for detecting lung metastases, particularly during the first 2 years. (Annals of Surgery, 154: 235–240 (1961).)

Cancer Chemotherapy National Service Center program reflects gains of past 6 years

The national program of research on cancer chemotherapy, coordinated by the Institute's Cancer Chemotherapy National Service Center, is focused on a single, well-defined objective, the discovery and application of drugs that can be used effectively for the control—hopefully the cure—of malignant disease. The tremendous growth of the program since its establishment in 1955 and the unprecedented progress made toward its goal have dictated a number of program changes, which both reflect the gains of the past 6 years and strongly suggest significant further advances in the months and years to come.

The initial screening of materials, perhaps the most crucial phase of the program, has been in transition for some time. Originally, candidate drugs were evaluated against three experimental mouse tumors. It was recognized from the beginning that so limited a screen would per se yield information of limited value. It might, on the one hand, select too many materials that would prove to be of little or no value in treating human cancer. More seriously, it might fail to detect activity in materials that would, if tested further, be found highly useful. The obvious solution to these problems of limitation was the inclusion in the screening mechanism of many more animal and laboratory test systems, which collectively could unearth previously unrecognized value in candidate drugs screened. Now, there are not three but about three dozen tumor systems available for screening purposes, some of which correlate to some degree with, and hence predict for, specific forms of human cancer. And in addition to experimental tumors in mice, rats, and hamsters, tissue culture is also used for screening purposes. As a consequence of the broadened base in primary screening activity, which now represents about 200,000 separate tests a year, half as many annually as were carried out in the first 5 years of the program, much more information is being made available on promising materials. Accordingly and appropriately, the number of materials entering the screening activity each year has been reduced from 50,000 to 40,000; at the same time, the number of agents moving through the program to the stage of clinical evaluation has risen sharply.

The tremendous output of effort over the past 6 years has maneuvered the chemotherapy program into the paradoxically desirable position of having many more worthwhile, promising materials ready for clinical evaluation than can be studied under the existing cooperative clinical research network, a far cry from the situation several years ago when the clinical program was being set up with virtually nothing new to test. Now the number of promising new agents and the increasing enthusiasm which the program has generated among physicians throughout the country have permitted the formation of many new cooperative clinical research groups and the initiation of a variety of new studies.

An important shift in the clinical program, apart from its growth, is reflected in the kinds of study that are now getting underway. Without the abandonment of any needed and significant clinical endeavor, emphasis is moving from large-scale studies of the known responsive types of cancer to broad spectrum investigations of new drugs against virtually all forms of the disease. This is being done in an effort to assure that no promising agent fails to be tested adequately. One important step in this direction was the establishment of three new regional cooperative groups, eastern, central, and western, which have been organized specifically for the purpose of assessing new agents against the greatest possible number and variety of human cancers. It is anticipated that as many as 6,000 patients per year will participate in these three group studies. The total number of patients entered into the clinical chemotherapy program doubled between 1959 and the present, and now stands at more than 18,000. This figure, and the number of drugs that have received some measure of clinical assessment—approximately 170—will continue to rise in the year to come at an increasing rate as the full impact of important program adjustments is felt.

STUDIES AT THE CELLULAR LEVEL

New technique reported for quantitative analysis of nucleic acid compounds

Drs. James C. Reid and Arnold W. Pratt, Laboratory of Physiology, have reported a new technique for the quantitative analysis of the composition of nucleic acid and mixtures of its metabolites.

The objective of their research is to find out whether the urine of leukemia patients contains detectable excretion of nucleic acid precursors, nucleotides and nucleosides, and to develop an analytical method of identifying and quantifying such compounds.

A new approach was sought to the quantitave determination of individual components of the mixtures obtained by chromatography of urine specimens, when the chromatographic technique was found to be unwieldy and lacking in precision. Drs. Reid and Pratt applied the mathematical technique of vector analysis, with the aid of an electronic computer, and obtained highly accurate results in the analysis of the ultraviolet spectra of synthetic mixtures of nucleotides. Similarly precise results were observed for a mixture of nucleotides obtained by chemical treatment of commercial RNA.

The investigators conclude that the "computational technique" will be useful in studies of disturbances of nucleic acid metabolism in patients with leukemia. (Biochemical and Biophysics Research Communications 3: 337–342 (1960).)

Grantee's study shows how tumor cells migrate within body of a host

Dr. Irving Zeidman, at the University of Pennsylvania School of Medicine is conducting studies to determine how tumor cells migrate within a host. He has now reported the results of experiments designed to learn what happens when a tumor cell passes from an artery into a capillary.

Dr. Zeidman performed this work with rabbit mesentery, the tissue which binds the intestine to the abdominal wall. Loops of small intestine were removed from the animals, and the attached mesentery was mounted on a microscope stage. After an arteriocapillary junction was located, cells from V_2 and Brown-Pearce carcinomas were injected nearby into the artery, and their movements were receorded in motion pictures.

Most of the cells paused at the junction, became elongated, then entered and passed through the capillary. A few cells did not change in shape, and were permanently arrested at the junction. The Brown-Pearce cells, although they were larger than the others, entered the capillary more frequently.

Dr. Zeidman concluded that the size of the cells had less influence on their movement than did their ability to elongate in the direction of the long axis of the capillary. (Cancer Research 21: 38–39 (1961).)

Factors studied that govern differentiation of epithelial cells

Knowledge of the factors that govern differentiation of normal cells is essential to understanding the loss of structural and functional organization by cancer cells.

A finding that the connective tissue environment influences differentiation of epithelial cells has been reported by Drs. Eugene J. Van Scott and Richard P. Reinertson of the Dermatology Branch.

The study included 11 individuals; 9 were skin cancer patients, 1 had mild psoriasis, and the other had no skin disorder. In a series of experiments, epithelial cells with and without theri connective tissue were transplanted to new sites in their own hosts. Thus, mucous membrane from the inner surface of the lower lip, scalp hair roots, and basal cell tumors were implanted in the back, and skin cells of the back and arm were implanted in the lower lip.

Only when connective tissue was included did the transplants survive and retain their original cellular characteristics. Otherwise, they degenerated, became keratinized (horny), or developed structural features that often resembled those of epithelium at the new site. (Journal of Investigative Dermatology 36: 109–131 (1961).)

Research on relationship of structure to function of nucleic acids reported

A report on research aimed at learning how the structure of nucleic acids is related to their function was presented by Dr. Herbert A. Sober, Chief of the Laboratory of Biochemistry, at the Fifth International Congress of Biochemistry, meeting in Moscow in August. Dr. Sober described work being done by himself and others in his laboratory in collaboration with colleagues of the National Institute of Arthritis and Metabolic Diseases.

Their work starts from the concept that heredity, as well as normal growth and repair, is governed by nucleic acids, large molecules composed of thousands of chemical units (nucleotides). The order in which these units are arranged appears to play a role in determining various characteristics of living things. For instance, a slight difference in sequence could alter essential features of viruses, bacteria, animals, and man.

It is logical to expect that there are differences in the nucleic acids of normal and malignant cells, and that identifying these differences may provide information about the causes and development of cancer. However, the sequence of units has not been worked out for any nucleic acid.

Dr. Sober and his associates begin attacking this problem by mixing nucleic acids with enzymes that split the molecules at certain places, thus breaking them into pieces that can be analyzed and identified by the techniques of chromatography and electrophoresis. The data make it possible to deduce the arrangement of only a few units at a time, but ways of handing larger pieces are being developed.

Employing another approach, Dr. Sober and his coworkers have been making artificial molecules containing several units, and studying their behavior. This phase of the investigation has already indicated that when seven or more units are linked, they begin to line up in the spiral configuration characteristic of intact nucleic acid chains.

Strain of human cells grown for first time in serum-free medium

A collaborative study of the growth of human skin in tissue culture was inaugurated about 8 years ago by scientists now of the Laboratory of Viral Oncology and colleagues of the tissue bank of the National Naval Medical Center. These investigators reported in 1956 that a strain of human epithelial cells had been isolated and maintained in a medium consisting of human serum, filtered chick embryo extract, and saline.

They now report that cells from this culture system have been adapted to grow rapidly in an entirely chemically defined, protein-free medium. This is the first time human cells have been adapted to grow in this synthetic medium, known as NCTC 109.

The task of adapting cells to the medium required a period of 2 years, in which the amount of human serum added to the nutrient was gradually reduced. At the time the report was prepared, monolayer cultures of cells, designated strain NCTC 3075, had been maintained in NCTC 109 for 22 months. Fluids were changed three times a week, and subcultures were made at weekly intervals.

Among the developments that were made to gain precise control of the culture technique was a modified procedure for cleaning glassware. Cells growing in specially cleaned flasks adhered to the glass in uniform sheets instead of clumps, and had a better appearance than those in flasks washed by routine methods.

The authors report that cells of the same strain also multiplied rapidly while growing suspended in the synthetic nutrient fluid in shaking flasks. After some modifications had been made in the original procedure, these constantly agitated cultures yielded larger numbers of cells than the static type.

Human cell lines growing in serum-free media are expected to be particularly useful in studies of the role of viruses in human neoplasms, because the media contain no biological products that would act as contaminants. (American Journal of Hygiene 73: 96–104 (1961).)

Institute grantees report new studies of cellular nucleic acid synthesis

Drs. E. Reich, R. M. Franklin, A. J. Shatkin, and E. L. Tatum, of the Rockefeller Institute, New York City, have reported studies which show that it is possible to differentiate viral RNA synthesis in a cell from the cell's own RNA synthesis. This observation in molecular biology is fundamental to an understanding of the living cell, including the abnormal cell that may develop into cancer.

Three experiments established this observation:

Normal mammalian cells grown in culture were incubated with Actinomycin D, an antibiotic, with the result that cellular RNA synthesis, but not DNA synthesis, was completely arrested.

Actinomycin D inhibited the multiplication of a DNA virus (vaccinia) in host cells.

The growth of an RNA virus (Mengo virus) in host cells was not inhibited by Actinomycin D.

Thus, the replication of viral RNA is distinguished from the replication of RNA which is controlled by cellular DNA or viral DNA. The observation that cellular DNA synthesis was not inhibited by Actinomycin D suggests that the cellular genetic apparatus remains intact. (Science 134: 556–557 (1961).)

Further studies of chromosomes in human leukemia reported

Two Philadelphia scientists, Drs. David A. Hungerford, the Institute for Cancer Research, and Peter C. Nowell, University of Pennsylvania, have reported their most recent studies of chromosomes in human leukemia.

The approach these scientists use is essentially to examine blood or bone marrow cells that have been grown in tissue culture for 3 or 4 days after being taken from patients. A year ago, they reported the observation of an abnormal chromosome in leukocytes from two chronic granulocytic leukemia patients. Soon afterward, a group of investigators in Edinburgh (Scotland) saw the same abnormality in many of the patients they studied.

The presence of this so-called Philadelphia chromosome has now been observed in 9 of 10 more chronic granulocytic leukemia patients. These patients were found to have the normal total of 46 chromosomes per cell, including the abnormal chromosome. The latter, as reported previously, is one that appears to have lost about half of its long arm. The investigators have tentatively decided that the anomaly is derived from the normal chromosome designated number 21 by a standard nomenclature now in use.

The abnormal chromosome was seen in cells taken from one patient at the time of diagnosis and in those taken from several others a few days after diagnosis. These findings, according to Drs. Hungerford and Nowell, suggest that the Philadelphia chromosome is a primary abnormality that may be related to the origin of leukemia rather than a secondary phenomenon arising during the course of the disease.

Other observations were reported on studies of chromosomes in acute leukemia. The majority of cells taken from seven patients were found to have normal sets of chromosomes. Though some numerical and structural aberrations were seen, they did not form any consistent pattern. They were, however, more common in cells from patients who had undergone intensive therapy for long periods than in cells taken from others whose treatment had not been initiated at the time or who had received treatment for only a short period.

Since the techniques now available for analyzing human chromosomes are relatively crude, the results reported by different investigators are often discrepant and their significance is difficult to assess. Nevertheless, the observation of the

Philadelphia chromosome in particular raises the possibility of detecting other abnormalities consistently when techniques are more refined. (Journal of the National Cancer Institute 27: 983–1035 (1961).)

Cytotoxic factor demonstrated in leukemic guinea pig material

Evidence of the presence of a cytotoxic factor in leukemic guinea pig plasma or spleen extract has been reported by Drs. Claus W. Jungeblut and Helen Kodza of the College of Physicians and Surgeons, Columbia University, New York City.

Normal guinea pig spleen cells growing in primary tissue culture were destroyed by plasma, spleen extract, or serum from leukemic guinea pigs. Neither normal plasma nor serum produced this effect. Furthermore, leukemic plasma did not produce cytotoxicity in other malignant cultures (leukemic guinea pig spleen cells and HeLa cells) or fetal cultures (human amnion cells and whole embryonic mouse cells). These findings suggest a certain degree of specificity of the effect.

The cytotoxic factor was filterable and stable to heat up to one-half hour at 65° C. It retained its potency at dilutions up to 1: 500, but the potency was not enhanced by serial transfers in tissue culture. Guinea pigs injected with culture fluids displaying cytotoxicity failed to develop leukemia but did develop the disease when challenged with leukemic plasma. (Proceedings of the Society for Experimental Biology and Medicine 104: 666–669 (1960).)

TUMORS IN LABORATORY ANIMALS

Way developed to produce in rats a type of lung cancer similar to man's

Dr. Mearl F. Stanton and Robert H. Blackwell, Laboratory of Pathology, have developed a way of producing in rats a type of lung cancer that is similar in cell structure and behavior to the type usually seen in man. Their work makes available a new tool for laboratory studies of lung cancer.

The experiments were designed to deposit a cancer-causing agent in or near lung tissue that had been damaged and was undergoing repair and regeneration. Such tissue was expected to be particularly susceptible to the effects of the cancer-causing agent.

Rats 5 to 7 months old received intravenous injections of a chemical (hexachlorotetrafluorobutane) that produced areas of infarction and dead tissue in the lungs, but no cancers.

However, lung cancers did develop when the chemical was mixed with an agent (3-methylcholanthrene) known to cause lung tumors in rodents, though the agent alone produced no malignant tumors in these experiments.

Some of the cancers produced by simultaneous injection of the two compounds appeared to have originated in damaged lung areas that had healed. Other cancers were so extensive when the lungs were examined that the site of origin could not be determined, but there were indications that all of them originated in damaged tissue.

The cancers spread from the lungs to many other organs: lymph nodes, kidneys, adrenal glands, heart, liver, and, in one animal, ovaries.

The success of this method supports the idea that damage and regeneration play a role in the development of experimental lung cancer. In addition, the procedure may be useful in testing agents suspected of causing lung cancer. (Journal of the National Cancer Institute 27: 375–407 (1961).)

Contagious tumor of hamster reported

Mrs. Darlene C. Brindley and Dr. William G. Banfield, Laboratory of Pathology, have reported studies of a contagious neoplasm observed in a 2-year-old golden hamster. This is only the fourth such animal tumor recorded in the scientific literature.

The tumor, a reticulum-cell sarcoma, arose spontaneously in the upper lip of the hamster. It was carried successfully through 12 transplant generations in randomly bred hamsters.

Contagiousness of the tumor was indicated by a contact exposure experiment in which the scientists caged 10 untreated animals with an equal number of inoculated animals. Obstruction of the larynx from submucosal growth resulted in the death of seven. Two others died from widesperad tumor metastases similar to those produced in animals injected with solid tumor transplants.

Tumor transmission also occurred when the animals' exposure to each other was limited by a wire screen separator. One of three animals exposed in this manner died of tumor obstructing the larynx. Tumors also developed in two out of five separately caged animals fed fresh tumor tissue.

Inoculations of blood, ascites fluid, and brain tissue from tumor-bearing animals produced solid tumors. Although malignant cells were not found in the brain of dying, tumor-bearing animals, they were abundantly present in the peripheral blood at this time. This probably accounts for the successful brain transplants. An attempt by the authors to produce tumor with cell-free filtrates has been unsuccessful. (Journal of the National Cancer Institute 26: 949–957 (1961).)

IMMUNOLOGY

Swedish scientists report evidence malignant cells share a common antigen

Dr. Bertil Björklund and his associates of the State Bacteriological Laboratory and St. Göran's Hospital, Stockholm, Sweden, have reported additional results of their continuing investigation of the concept that malignant cells share a common antigen not possessed by normal cells.

The antigen was obtained by processing human carcinoma tissue in accordance with a procedure devised previously. The antigen is a lipoprotein (combination of fat and protein), is insoluble in all solvents tested, and is inactivated by prolonged exposure to temperatures greater than 40° C., treatment with enzymes that break down protein, or grinding for hours at temperatures much higher than —70° C.

An antiserum has now been prepared by immunizing a horse over a period of years with antigen from several hundred pooled human tumors, representing 16 types of primary carcinoma or metastases. The pooled tissue was expected to contain a relatively large amount of the common antigen, if one existed, but only small amounts of individual normal tissue antigens.

The antiserum destroyed tissue cultures of four established lines of malignant cells, HeLa, Detroit-6, conjunctiva, and heart. Such cultures were similarly affected by antiserum that had been mixed with normal tissue preparations.

However, when the antiserum was first reacted with antigen from any one of 60 carcinomas or with any of the malignant cell lines, it lost its capacity to destroy malignant cells in tissue culture. Furthermore, the loss was of the same extent with each of the 60 carcinomas.

The authors conclude that this finding supports the concept that the same antigen was present in each of the carcinomas employed in this study. (Journal of the National Cancer Institute 26: 533–545 (1961).)

Experiments show that parity affects response of mice to transplants

Scientists of the Laboratory of Biology have reported the results of experiments designed to determine whether parity (bearing offspring) has any effect on the response of mice to transplanted tumors.

Tolerance and resistance to transplants in mice are hereditary characteristics, governed by a group of genes. Unless the strongest of these genes is alike in the donor and recipient, a transplant usually does not "take."

Drs. Edward J. Breyere and Morris K. Barrett tested the effect of parity by transplanting a tumor from C3H mice into BALB/c females that had borne offspring. The strongest of the genes governing transplantation is not alike in these strains.

The C3H tumor grew in and killed almost 60 percent of BALB/c females whose offspring had been sired by C3H males; the percentage of "takes" was highest in the females that had borne more than one litter. The tumor did not "take" in BALB/c virgins. Nor did it "take" in more than 1 percent of BALB/c females whose litters were sired by either BALB/c or DBA/2 males.

The results indicate that parity induced tolerance only to a tumor from the strain of mice that sired the offspring.

These findings are of particular interest in light of the growing importance of research on the possible relationship between resistance to transplants and the role of immunity in resistance to cancer. (Proceedings of the American Association for Cancer Research 3: 212 (1961).)

Scientist reports on investigation of drug-induced immunological "tolerance" in mice to tumor homografts

Knowledge of factors that control susceptibility to cancer transplantation is important not only to an understanding of immunity to cancer but also to the development of practical methods of conditioning an individual to accept a genetically incompatible transplant.

Miss Delta Uphoff, Laboratory of Biology, has now reported preliminary results of investigating drug-induced immunological "tolerance" in mice to tumor homografts.

The study originated in Miss Uphoff's earlier observations that the drug, methotrexate, protects mice from the lethal effect of a homograft reaction following total-body irradiation and the inoculation of genetically incompatible bone marrow. The mice in which the graft versus host reaction was suppressed were found to be chimeras.

Since the methotrexate inhibited a graft versus host reaction, it was reasoned that "tolerance" to homotransplants could be produced by pretreatment with a combination of the drug and a viable cell suspension from an appropriate foreign strain. In the present study, mice were rendered "tolerant" to tumor transplants from mice of an unrelated strain by pretreatment with methotrexate and a tissue brei of spleen and thymus of the donor strain. Progressive tumor growth was not observed in mice pretreated with drug or tissue brei alone.

Induction of "tolerance" was accomplished in three different strain combinations which varied in their genetic incompatibility. It was found that to induce the "tolerant" state, pretreatment over a prolonged period of time was necessary.

In her report, Miss Uphoff stressed the need for comparatively simple test systems for determining the optimum pretreatment method for inducing "tolerance." She noted that marrow transplantation in the lethally irradiated mouse was to complicated a test system, and that tumor transplation, although less critical than skin transplantation, made possible the trial of more types of treatment schedules than would otherwise have been feasible. (Plastic Reconstructive Surgery and Transplantation Bulletin 28:110–114 (1961).)

Part 2. Leukemia[2]

Scientific interest in the leukemia problem is stronger now than it has ever been. Encouraged by the work of a few pioneers, and fortified by an unprecedented outpouring of financial support from public and private agencies, hundreds of scientists, working separately and in groups, are attacking leukemia from all sides. Theirs is a monumental task: to find ways of extending the limited progress already made in caring for leukemia patients and to determine the causes of leukemia so that ways of preventing the disease may be found.

The human leukemia problem appears to be growing. There were 10,816 deaths from leukemia in the United States in 1955, slightly more than four times the number recorded in 1930. During the same period, age-adjusted death rates for leukemia rose from 2.9 to 8 per 100,000 for white males and from 2.1 to 5.3 for white females, the increase being greatest among persons 50 years old and above. These figures, of course, reflect an identical rise in the incidence of leukemia. Why the record should show a higher incidence of the disease in 1955 than in 1930 is not altogether clear. It seems likely that better case finding is partly responsible, but the size of this share remains in doubt.

Like other forms of cancer, and other diseases as well, leukemia occurs often enough among people in special situations to enable epidemiologists to identify some potential etiologic factors and assess their importance. There are, for example, records of more than 150 families in which at least 2 members had leukemia. In some, four or five cases occurred. However, no large-scale survey has given clear-cut evidence that heredity contributes directly to the incidence of leukemia. Possibly, only a susceptibility is inherited, and this would be hard to demonstrate. Another possibility is that exposure of entire families to the same leukemogenic agent may account for familial cases.

Ionizing radiation is one established cause of leukemia, and a few cases have been attributed to the effects of chemicals, principally benzol. An unusual incidence of leukemia has been recorded among survivors of the atomic bomb explosions in Japan, radiological workers (including physicians), and persons who received radiotherapy, including X-ray and radioisotopes, for conditions other than leukemia. Whether children whose mothers received pelvic X-rays during pregnancy are subject to an increased risk is considered debatable.

In fact, the extent of the radiation-and-leukemia problem as a whole is somewhat uncertain. When the mechanism by which radiation causes leukemia is better understood, the risk it presents may be more clearly appraised. Nevertheless, the events in Japan did suggest that in a population receiving at least 100 rads in a single dose, 100 cases per million persons exposed can be expected to occur in 10 to 15 years following exposure. Nearly all the cases in Japan were acute leukemias and chronic granulocytic leukemias. But neither this nor any other human experience with radiation indicates whether there is a threshold dose—one too small to alter the risk of developing leukemia. As a result, the leukemogenic effects of small doses, such as those used in diagnosis, cannot be estimated.

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[2] This report summarizes current trends in research on causes and treatment of leukemia.

What happened in Japan also emphasizes the fact that susceptibility to radiation-induced leukemia varies from one individual to another. The incidence reached 1 per 100 among persons who received the largest doses. Obviously, establishing why the other 99 did not develop leukemia would go a long way toward clarifying the role of radiation and its possible relationship to other factors suspected of causing leukemia.

Epidemiologists, and their colleagues in other areas of leukemia research, are now actively investigating the "clusters" of leukemia cases, primarily among children, that have been noticed in a growing number of population centers in all parts of the country. Though these may not be new phenomena, they were seldom, if ever, reported before. Lately, news of their occurrence has come from places in Wyoming, Utah, New Jersey, Georgia, Illinois, and Hagerstown, Md., where the National Cancer Institute is conducting a long-term cancer epidemiology survey.

A particularly notable episode involved the community of Niles, Ill., a suburb of Chicago. There, eight cases of acute leukemia were diagnosed between September 1957 and August 1960, in children who attended the same parochial school or who had brothers, sisters, or close friends in the school. The 8 cases in 3 years represented about 20 times the normally expected number in a community with a population of 20,000. Public Health Service personnel from the Communicable Disease Center, Atlanta, and the National Cancer Institute checked the Niles cases, but their findings did not suggest any relationship between leukemia and heredity, radiation, prior illness, or any other factor that could be investigated on the spot.

VIRUSES AND LEUKEMIA

To some scientists, the events in Niles look like another piece of evidence favoring viruses as a cause of leukemia, a concept that once again is prominent after a long period in which it received little attention. Though much work remains to be done before viruses can be related to the etiology of human leukemia, some valuable guidelines are coming from studies of the disease in animals, principally fowl and mice.

The fowl leukosis complex includes two highly malignant forms of leukemia—erythroblastosis and myeloblastosis—and a related group of neoplasms classified as "lymphomatosis." These forms and several variants may occur separately or in almost any combination, but visceral lymphomatosis is the only one that occurs commonly under natural conditions. It is, in fact, widespread enough to pose a definite economic problem in commercial poultry breeding. Two leading investigators of fowl leukosis, Dr. Joseph W. Beard, Duke University, and Dr. Ben R. Burmester, U.S. Department of Agriculture, East Lansing, Mich., have formulated a tentative explanation of how the fowl viruses are interrelated.

To begin with, visceral lymphomatosis is a contagious disease. The virus that causes it is present in the excreta and saliva of infected birds and therefore may reach uninfected birds by direct contact or through contaminated food and water. In addition, the virus is passed from mother to offspring in the egg. Since some progeny also receive maternal antibodies, the virus may persist in a latent state in birds that show no signs of having lymphomatosis. This has demonstrated that immunizing the mother is a way of protecting newborn chicks at the time when they are ordinarily most susceptible.

Neither erythroblastosis nor myeloblastosis is contagious and they occur rarely under natural conditions. The various avian leukosis viruses have some important distinctive properties (such as the high activity of the enzyme adenosine triphosphatase in the myeloblastosis agent), but they are immunologically related. When chickens are immunized against erythroblastosis or myeloblastosis virus, their serum neutralizes both, and when they are immunized against myeloblastosis virus, their serum contains antibodies to the visceral lymphomatosis virus. Also, many investigators have noticed that fowl inoculated with material from one type of avian neoplasm occasionally develop another type instead.

Together, all these observations indicate to Drs. Beard and Burmester that the noncontagious forms of leukosis may be caused by variants of the visceral lymphomatosis virus that have lost their ability to spread to new hosts. Thus, studies of the fowl leukosis complex have shown that neoplastic viruses, like others, may be antigenic in their natural hosts, may travel along conventional routes of transmission, and possibly undergo variation.

STUDIES OF MOUSE LEUKEMIA

Some recent results of research on mouse leukemia have brought scientists within striking distance of the human problem. The work has moved rapidly since 1951, when Dr. Ludwik Gross, Veterans' Administration hospital, New York, succeeded in transmitting one form of mouse leukemia with cell-free material. A number of other viruses capable of inducing various forms of leukemia in mice and rats were soon isolated and shown to have some interesting properties. One isolated by Drs. H. M. Schoolman and Steven O. Schwartz, Hektoen Institute, Chicago, is unique in that it has been recovered in appreciable quantities only from the brains of mice bearing the leukemia it induces. Dr. Charlotte Friend, Memorial Sloan-Kettering Cancer Center, New York, isolated one that stimulates production of antibodies in mice and rabbits. Thus, she has been able to prepare a vaccine that keeps mice from developing the leukemia-like disease that the virus ordinarily induces. Dr. A. Graffi, Institute for Medicine and Biology, Berlin, isolated another that causes myelocytic leukemia rather than the lymphocytic type usually seen in mice.

The relationships of all these agents to one another are at present only poorly understood. Electron microscope studies have shown that the viruses resemble one another in size and structure. Some of them can cause more than one form of leukemia. A variant may occur, for example, in a mouse whose thymus has been removed. The fact that the mouse leukemia viruses generally do not stimulate strong immunological reactions; e.g., formation of antibodies, in their natural hosts has been an obstacle in immunological and chemical studies of the interrelationships among the viruses.

Some investigators have found evidence of a link between ionizing radiation and leukemogenic viruses. Both Dr. Gross and Dr. Henry S. Kaplan, Stanford University, have reported that cell-free material from a radiation-induced lymphoid tumor produced the same neoplasm when inoculated into nonirradiated, susceptible hosts.

At the National Cancer Institute findings obtained in studies of a mouse leukemia have enabled scientists to begin investigating the viral etiology of leukemia directly in man. The mouse leukemia is induced by an unusual virus that Dr. John B. Moloney isolated 3 years ago from a mouse sarcoma. Unlike other murine leukemia viruses, which induce the disease in varying percentages of mice of a few susceptible strains, the Moloney virus causes leukemia in essentially 100 percent of mice of all strains tested so far, regardless of their age at the time of inoculation, and in rats as well. Dr. Moloney has established that the virus contains ribonucleic acid (RNA); and, with the aid of the electron microscope, Dr. A. J. Dalton, National Cancer Institute, has estimated the size of the virus particle and described its structure. Dr. Robert A. Manaker, National Cancer Institute, has succeeded in growing the virus in tissue culture, which has been difficult to do with other mouse leukemia viruses. Dr. Lloyd W. Law, National Cancer Institute, has shown that the virus is passed from parents to offspring most effectively in the mother's milk.

Now an electron microscope study has revealed the presence of virus particles in the blood of rats bearing the Moloney leukemia, and a centrifugation scheme has been devised for extracting the virus in essentially pure form. The availability of such highly purified material paves the way for studying the biological, biochemical, and immunological properties of the virus with greater precision than has hitherto been possible.

This work has prompted a group of National Cancer Institute investigators to try using the same techniques in a search for viruses in the blood of human leukemia patients, and in this way to obtain at least preliminary evidence linking viruses to the etiology of human leukemia. Through the electron microscope, scientists at other institutions have already found virus-like particles in lymphoid and myeloid tissue from a few leukemia patients.

Proof that such particles represent viruses that cause leukemia requires, as a start, evidence that they are present in large numbers of cases and never (or only seldom) in normal individuals, and that, when isolated and assayed for biological activity, they will induce leukemias or other recognizable lesions in suitable model systems. Since viruses of all kinds occur so commonly in man and other species, the assay procedures need to be integrated with serological and immunological techniques as a means of correlating the results with the starting material.

ABNORMALITIES IN LEUKEMIC CELLS

At the present time, there is little more understanding of the fundamental nature of leukemia than of its etiology. Most scientists agree that, whatever the cause, leukemic cells must be basically, that is, qualitatively, different from their normal counterparts. On this rationale, many studies have been made of the morphology and chemistry of normal and malignant leukocytes.

However, the only abnormalities found so far have been quantitative. The best known is the low activity of the enzyme alkaline phosphatase in chronic granulocytic leukemia. This occurs consistently enough to be a useful criterion for diagnosis, and was detected long before disease was evident in Japanese atomic-bombing survivors who eventually developed granulocytic leukemia. Nevertheless, the fundamental significance of this enzyme defect is still to be determined. Lack of an enzyme has been suggested as the basic disorder in leukemia, but there is little concrete evidence to support the idea.

Other quantitative chemical differences between normal and leukemic cells have been reported, with respect to their content of such substances as nucleic acids and folic acid. In addition, the effect of leukemia on the host has been measured, for example, in terms of serum protein and vitamin alterations. Most of the findings are presently regarded as concomitants of rapid cellular proliferation, accelerated metabolism, or the consequences of advancing disease. As a result, it has not been possible to design drugs that will attack leukemic cells without damaging normal tissue as well.

PROGRESS IN TREATMENT

Nevertheless, the years since 1948 have been an era of substantial progress in treatment of leukemia patients. The lives of many can now be prolonged and made more comfortable by drug treatment, combined with supportive therapy for complications such as hemorrhage, infection, and anemia.

The best results have been achieved in managing acute leukemia in children. Reports from institutions handling large numbers of cases show that 50 percent of children treated with antimetabolites and steroid hormones survive 11 to 13 months from the onset of disease and 10 percent survive more than 20 months. Before present methods of therapy came into use, 50 percent survived just 4 months and only 10 percent survived as long as 11 months.

In contrast to the improved survival in children, there has been little overall improvement among adult acute leukemia patients, the difference being attributable to adults' poor response to treatment. Dr. Emil Frei III, National Cancer Institute, has reported that patients who respond, regardless of their age, survive almost three times as long as those who do not. As a rule, treatment of acute leukemia patients 2 to 15 years old produces complete remission in 35 percent and partial remissions in another 25 percent, but only 10 to 20 percent of adults have a complete remission resulting in prolonged survival.

The chronic leukemias present a different situation. Even without treatment, the average chronic leukemia patient survives 3 to 5 years and some live considerably longer. Though a high percentage of patients has a remission following treatment, not all investigators agree that survival is prolonged significantly. Nevertheless, life is substantially more comfortable for patients who respond to therapy.

Hidden behind the statistics, but well known to every clinician who cares for leukemia patients, is a veritable forest full of unsolved and partly solved problems. There is no way of predicting whether any one patient will respond to treatment. The patient who does not improve after receiving one drug may have a remission when another is given. When a remission does occur, it may be partial or complete, but it is always temporary, lasting a few weeks or months, rarely longer. There is little likelihood that the disease can be suppressed again with the aid of a drug that has already produced one remission, unless it is given in doses so large that severe side effects result. The chances of success with another drug of the same class are equally small. But when a drug of another class is substituted, a response may be obtained. Thus, a patient may have more than one remission, though each will be shorter and less likely to occur at all, than the preceding one. When all drugs known to influence the course of leukemia have failed, new agents are tried and occasionally prove beneficial for some patients.

For the most part, and this is especially true with respect to acute leukemia, the few drugs introduced in the early days of chemotherapy are still the best ones available. They include the folic acid antagonists (aminopterin and amethopterin), a purine antagonist (6-mercaptopurine), the steroid hormones (prednisone and prednisolone, which are now preferred over cortisone), and occasionally ACTH. Having no new drugs that are substantially better, clinicians are trying to learn how to derive the greatest possible benefit from those whose value has been proved. This means evaluating the merits of various dosage schedules, comparing the results of continuous and intermittent therapy (in which treatment is suspended when a remission begins and resumed at the first sign of a relapse), and judging the merits of using drugs individually and in combinations.

Such decisions are not easily made when the course of the disease and the results of therapy vary from one patient to another. They are best made on the basis of data from statistically controlled studies of large numbers of patients treated uniformly. Many studies of this kind have been completed or are now being conducted by cooperative clinical groups under the sponsorship of the Cancer Chemotherapy National Service Center, National Cancer Institute.

COMBINATION THERAPY

Summarizing one conducted by the Acute Leukemia Group B, Dr. Emil Frei III, National Cancer Institute, reported that combined treatment with amethopterin and 6-mercaptopurine produced remissions in a higher percentage of children than did treatment with either drug alone. However, the median duration of remissions and the overall survival were substantially the same for those receiving the combination and those given amethopterin followed by 6-mercaptopurine or the reverse. When patients received the drugs in sequence, their chances of responding to the first and second courses were equally good, thus indicating that new drugs can be tested effectively in patients with advanced disease.

Eventually, no matter how skillfully the clinician employs the therapeutic weapons he has, every leukemia patient enters a terminal stage. Treating a group of such patients with a new drug that proved to have no value, the Acute Leukemia Group B demonstrated that a substantial number of them showed temporary improvement even in the absence of effective therapy. Thus, the clinicians gained a little more insight into the natural history of acute leukemia.

The reason why only a relatively small percentage of adult acute leukemia patients responds to drug treatment is not fully understood but may be related to the predominance of granulocytic leukemia. An overwhelming share of acute leukemias in children, in contrast, is lymphocytic. Contrary to a long-standing impression, a substantial fraction of all adult leukemias is acute. These patients rarely respond to antifolic therapy, though about one in three may have a remission of some kind when given 6-mercaptopurine. A higher remission rate has been observed by Dr. Emil Freireich, National Cancer Institute, in a clinical trial of a new drug, methyl glyoxal bis guanylhydrazone, but too short a time has elapsed since the study began to judge the results in terms of duration of remission or effect on survival.

The drugs that are least useful in acute leukemia, the alkylating agents, are the principal components of therapy for the chronic leukemias. These include the nitrogen mustards, their derivatives, and the mustardlike compounds, grouped together because they all seem to act by combining with essential substances in cells, thus preventing mitosis. Aside from this generalized description, little is known of the precise mechanisms by which the alkylating agents work. Their effects resemble those produced by ionizing radiation, either from an external source or from isotopes given internally. Prior to the advent of chemotherapy, these modalities were the chief means of treatment of chronic leukemias, and they still are used frequently.

Research on alkylating agents has produced two drugs whose relative selectivity makes them strikingly different from most of the compounds now available for cancer chemotherapy. One is Chlorambucil, which has an affinity for lymphocytic tissue; the other is Myleran, which acts somewhat preferentially on granulocytic tissue. They are, of course, most useful in the corresponding types of chronic leukemia, though each is also of some value in the other type. Their relative specificity is one of the reasons why they produce fewer severe side effects than do other alkylating agents.

Undesirable side effects and drug resistance still present unavoidable hazards along the path to more effective treatment of leukemia patients. All the drugs now in use, with the exception of the steroids and ACTH, damage the bone marrow to a greater or lesser extent, depending on the dosage, though some patients tolerate them better than others.

Other tissues, especially the rapidly dividing cells that line the gastrointestinal tract, are also harmed. The hormones, in contrast, appear to stimulate bone-marrow activity, but they do produce some characteristic side effects at other sites. The steroids have been shown experimentally to destroy lymphoid tissue, but they have a broad range of other effects that cannot presently be explained.

Some investigators take the view that it is necessary to give drugs to the point of toxicity in order to induce a remission. Others have shown that good results can be achieved without such procedures. All but the most severe (and ultimately fatal) side effects can usually be reversed by reducing drug dosage, lengthening the interval between doses, or suspending treatment temporarily. No technique has been devised that will minimize the side effects of drugs without also counteracting their therapeutic action. This is what happens when, for example, citrovorum factor (folinic acid) is used to relieve the toxicity of treatment with folic acid antagonists.

MARROW TRANSPLANTS

Quite possibly, the extensive research now in progress on methods of circumventing radiation damage may be equally applicable to chemotherapy. One line of investigation in this area is concerned with replacement of bone marrow. Though marrow transplants between genetically compatible animals present no problem, ways of coping with immunological reactions need to be found before such procedures can provide lasting benefits in man. Nevertheless, marrow replacement following whole-body radiation therapy has been tried in a limited number of leukemia patients. Dr. E. Donnall Thomas, Mary Imogene Bassett Hospital, Cooperstown, N.Y., reported that all but one of six patients died of bacterial infections, thus raising still another difficulty requiring attention. Since tissues other than the marrow are also highly sensitive to radiation, chemicals are being sought that will protect them without also rendering leukemic tissue insensitive.

There are two forms of drug resistance in leukemia, differentiated by the time at which they arise. The disease is classified as inherently resistant when it cannot be influenced even from the outset of treatment. The other form is acquired, and develops after the disease has already responded to some kind of treatment.

Some progress has been made in understanding the basis of acquired resistance. Dr. Law, National Cancer Institute, has shown that a transplantable mouse leukemia becomes resistant as a result of random mutation. That is, by mutation some of the leukemic cells become resistant; the drug is merely a selective force, destroying the still-sensitive cells so that the tumor eventually consists of nothing but resistant ones. He and others at the National Cancer Institute and elsewhere are investigating the biochemical basis of drug resistance in the hope of finding ways to overcome it.

Dr. Jack D. Davidson, National Cancer Institute, has reported that mouse leukemia cells (in vitro) resistant to 6-mercaptopurine do not convert the drug to a derivative that appears to be responsible for its activity in sensitive cells. Resistant cells had little or none of an enzyme that participates in the conversion process. Other investigators have shown that mouse leukemia cells resistant to amethopterin have an increased amount of an enzyme whose activity is blocked by the drug in sensitive cells. Many other mechanisms of resistance have been identified in microbial systems and animal tumors, but little is known about the biochemical basis of drug resistance in man.

COMPLICATIONS OF LEUKEMIA

One of the few axioms in leukemia therapy is that complications are best managed by controlling the leukemic process. The next best way is to give the patient adequate supportive treatment, and this, in fact, often holds a serious situation in check long enough for antileukemia drugs to take effect. The need to cope with both leukemia itself and the complications it causes has given rise to the concept of total care, as set forth by Dr. Sidney Farber, Children's Cancer Research Foundation, Boston, a pioneer in chemotherapy.

It is a paradox that prolonged life provides an increased opportunity for the occurrence of complications and that many of them are caused directly or indirectly by drugs used against leukemia. By depressing the production of blood platelets in the bone marrow, drugs may provoke bleeding, or by lowering resistance, they may provide an environment in which infections develop easily. Fortunately, the means of dealing with such complications have been improved in recent years.

Severe hemorrhage has always been one of the principal immediate causes of death in leukemia. Some investigators have reported that patients do not bleed profusely unless the number of platelets in their blood is critically low. On the other hand, many patients with serious platelet deficiencies do not bleed. Though the tendency to hemorrhage thus appears to depend not only on platelet status but also on other factors involved in clotting, little progress has been made in determining which ones are responsible. However, bleeding can be controlled temporarily by giving platelet transfusions.

An efficient way of obtaining and administering platelets has now been developed by Dr. Allan Kliman, Division of Biologics Standards, National Institutes of Health, in collaboration with National Cancer Institute investigators. By means of a "donor plasmapheresis" technique, platelet-rich plasma is rapidly separated from whole blood and given to patients while it is still fresh and therefore most likely to be effective. The principal advantage is that the red cells can be returned immediately to the donor, who can, as a result, give blood far more often than was hitherto possible. This reduces the number of donors per patient and the chance of infection. One donor may be able to supply all the platelets required by a child. Pooled plasma from several donors is used to meet the larger transfusions required by adults. The plasma obtained this way has afforded effective temporary control of bleeding in a high percentage of patients without provoking resistance to transfusions.

Overwhelming infections are another frequent cause of death in leukemia. Like other complications, they occur most often when all methods of managing the disease have been exhausted and patients are in a terminal stage. At this point, infection is not easily controlled. At other times, infections of bacterial and fungal origin are more readily disposed of, thanks to the use of antibiotics. A National Cancer Institute study has shown that *Pseudomonas* (bacteria) and fungal infections have become increasingly common. Fever also occurs in leukemia patients, and the results of one National Cancer Institute investigation emphasized the value of regarding it as a sign of infection, requiring immediate treatment.

ANEMIA

Autoimmune anemia—arising when patients develop antibodies to their own red cells—is a frequent complication of chronic lymphocytic leukemia and usually can be corrected by treatment with steroid hormones. Often, the presence of autoantibodies cannot be demonstrated but may be assumed. In other forms of leukemia, autoimmunity is rare but anemia is nevertheless common. There is little agreement on the causes of anemia in these cases, but the factors that may be involved include reduced production of red cells because the bone marrow is overcrowded by proliferating leukemic tissue, excessive destruction of red cells by a mechanism other than autoimmunity, and depopulation of the marrow by the leukemic process or the effects of therapy. Blood transfusions are useful for temporary control of anemia, but a high hemoglobin level can rarely be maintained for long unless the disease is controlled by drug treatment. Occasionally, the transfusion itself induces a remission in acute leukemia.

In any leukemia patient, involvement of a vital organ may bring on a particularly troublesome situation. For example, infiltration of the brain by leukemic cells results in a condition known as the meningeal syndrome, a phenomenon that has been seen more often since the advent of chemotherapy than it was previously. The difference has been attributed at least in part to success in prolonging the lives of patients, particularly children, in whom the syndrome is seen most frequently. It may occur at any stage of the disease, even during a remission.

National Cancer Institute scientists who have studied and described the meningeal syndrome in detail have reported that the failure of drugs given by conventional routes to achieve therapeutic concentrations in the cerebrospinal fluid allows leukemic cells to become established in the brain and elsewhere in the central nervous system. Using dogs and dogfish as models, Dr. David P. Rall, National Cancer Institute, has found that compounds which do penetrate the "blood-brain" barrier are removed by outflowing cerebrospinal fluid more rapidly than they enter it.

For some time, scientists at the National Cancer Institute and other institutions have been injecting folic-acid antagonists directly into the cerebrospinal fluid as a means of arresting the meningeal syndrome. The work done by Dr. Rall and his colleague has suggested that when this procedure is used, the bone marrow and other organs can be protected by citrovorum factor administered systemically without nullifying drug action against leukemic cells in the central nervous system.

CONCLUSION

In the effort to cure and ultimately to prevent leukemia, two recent advances stand out as key contributions. One is the availability of drugs that suppress leukemia temporarily. The other is the recognition that viruses are an important cause of the disease in mammalian species.

A major share of leukemia research now underway is aimed at extending these findings. The effort in chemotherapy is to lay down a rational basis for drug development in the hope that new drugs will be increasingly effective in controlling the disease for longer and longer intervals. Other research is just beginning the arduous task of learning whether viruses are a cause of human leukemia. In the unsolved leukemia puzzle, these fundamental problems look like the most important pieces and, accordingly, are receiving the most attention.

FRIDAY, FEBRUARY 9, 1962.

MENTAL HEALTH ACTIVITIES

WITNESSES

DR. R. H. FELIX, DIRECTOR, NATIONAL INSTITUTE OF MENTAL HEALTH

DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

RICHARD L. SEGGEL, EXECUTIVE OFFICER, NATIONAL INSTITUTES OF HEALTH

G. A. VAN STADEN, EXECUTIVE OFFICER, NATIONAL INSTITUTE OF MENTAL HEALTH

Object classification

[In thousands of dollars]

	1961 actual	1962 estimate	1963 estimate
PUBLIC HEALTH SERVICE			
11 Personnel compensation:			
Permanent positions	4, 617	6, 198	6, 832
Positions other than permanent	557	571	580
Other personnel compensation	84	73	73
Total personnel compensation	5, 258	6, 842	7, 484
12 Personnel benefits	554	700	756
21 Travel and transportation of persons	485	550	580
22 Transportation of things	53	56	82
23 Rent, communications, and utilities	141	90	111
24 Printing and reproduction	44	12	17
25 Other services	1, 745	2, 088	2, 554
Payment to "National Institutes of Health management fund"	4, 180	4, 974	5, 398
26 Supplies and materials	411	489	524
31 Equipment	375	502	564
41 Grants, subsidies, and contributions	78, 591	87, 046	108, 729
Total, Public Health Service	91, 837	103, 349	126, 799
ALLOCATION TO SAINT ELIZABETHS HOSPITAL			
11 Personnel compensation:			
Permanent positions	70	71	71
Positions other than permanent	----------	3	3
Other personnel compensation	4	5	5
Total personnel compensation	74	79	79
12 Personnel benefits	5	8	8
23 Rent, communications, and utilities	6	8	8
26 Supplies and materials	1	4	4
Total, Saint Elizabeths Hospital	86	100	100
Total obligations	91, 923	103, 449	126, 899

Personnel summary

	1961 actual	1962 estimate	1963 estimate
PUBLIC HEALTH SERVICE			
Total number of permanent positions	701	965	1, 031
Full-time equivalent of other positions	79	78	80
Average number of all employees	728	927	1, 016
Number of employees at end of year	885	993	1, 041
Average GS grade	7. 5	8. 0	8. 0
Average GS salary	$6, 691	$6, 989	$6, 997
ALLOCATION TO SAINT ELIZABETHS HOSPITAL			
Total number of permanent positions	14	14	14
Average number of all employees	14	14	14
Number of employees at end of year	14	14	14
Average GS grade	4. 4	5. 1	5. 1
Average GS salary	$4, 713	$4, 846	$4, 846
Average salary of ungraded positions	$5, 591	$5, 591	$5, 591

Program and financing

[In thousands of dollars]

	1961 actual	1962 estimate	1963 estimate
Program by activities:			
1. Grants and related contracts:			
(*a*) Research	30,962	42,748	54,437
(*b*) Fellowships	2,217	2,892	2,892
(*c*) Training	39,470	34,656	44,650
(*d*) State control programs	5,942	6,750	6,750
Total, grants and related contracts	78,591	87,046	108,729
2. Direct operations:			
(*a*) Research	7,860	9,153	9,775
(*b*) Collaborative studies	1,685	2,051	2,573
(*c*) Training activities	122	317	596
(*d*) Professional and technical assistance	1,813	2,114	2,122
(*e*) Review and approval of grants	1,504	2,047	2,413
(*f*) Administration	447	648	691
Total, direct operations	13,431	16,330	18,170
Total program costs [1]	92,022	103,376	126,899
Change in selected resources [2]	−99	73	
Total obligations	91,923	103,449	126,899
Financing:			
Comparative transfers to other accounts	129		
Unobligated balance lapsing	3,709	5,371	
New obligational authority	95,761	108,820	126,899
New obligational authority:			
Appropriation	100,900	108,876	126,899
Transferred to—			
"Construction of mental health-neurology research facility" (42 U.S.C. 292)	−5,139		
"Operating expenses, Public Buildings Service," General Services Administration (75 Stat. 353)		−56	
Appropriation (adjusted)	95,761	108,820	126,899

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[1] Includes capital outlay as follows: 1961. $386,000; 1962, $462,000; 1963, $564,000.

[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1960, $441,000 (1961 adjustments −$23,000); 1961, $319,000; 1962, $392,000; 1963, $392,000.

GENERAL STATEMENT

Mr. FOGARTY. The committee will come to order.

We have before us this morning the request for mental health activities. Dr. Felix, do you have a statement for the committee?

Dr. FELIX. Mr. Chairman, I have submitted a prepared statement. I would like, if it is agreeable with the committee, to make a few comments which I hope will enlarge upon this some and give you some additional information.

(The prepared statement of Dr. Felix is as follows:)

STATEMENT BY DIRECTOR, NATIONAL INSTITUTE OF MENTAL HEALTH, PUBLIC HEALTH SERVICE, ON MENTAL HEALTH ACTIVITIES

Mr. Chairman and members of the committee:

I am appearing before you for the 17th consecutive year. I believe I can say that these years will prove, in retrospect, to have been as momentous in their impact upon our traditional ways of dealing with the mental disorders as were the years of the Renaissance to art and the humanities, and of the Industrial Revolution to the economic life of the Western World.

Both the Renaissance and the Industrial Revolution came at the end of long periods of stagnation. Both were periods of great social change that, judged in retrospect, in a very literal sense remade the world of man. As a result of these changes, man's attitudes toward man were altered, as were his concepts concerning the nature of man and man's place in the universe. Both the Renaissance and the Industrial Revolution were characterized by great activity, creativity, and experimentation. And when these periods of change were over, and the processes that had been at work evaluated, it was impossible for the Western World ever again to live by the outmoded ideas and inadequate tools of the medieval world.

I shall not press for a close examination of the resemblances between these two great periods of history and the decade and a half that have just passed. Those of you who are historians would soon find evidence enough to disprove the analogy. And as a physician and administrator working in the field of the mental disorders and for mental health, I cannot point to any single discovery as far-reaching in its effects as was Harvey's demonstration of the circulation of blood, or the development of the first textile mills in England.

Nevertheless, the ferment, the activity, the eagerness, and the determination to bring about changes that have recently characterized our field suggest the type of intellectual, emotional, and scientific activity that has enabled man to develop new approaches to problems that had been considered insolvable.

We have finally recognized, in a very profound way, the social and medical problems created by our traditional way of dealing with the severely mentally ill; which has been to place them in social quarantine and to provide them with less than adequate care.

I believe that our recognition of the enormity of the tasks we face, as a consequence of the many decades of these traditional patterns of care, has become part of our national consciousness and conscience. In these hearings and in others like them in every State capital of the land, in the meetings of hundreds of medical societies and other professional groups, in meetings of a wide variety of citizen groups, in meetings of the 750 affiliates of the National Association for Mental Health, one fact stands out. Until recently, we have treated those of our severely mentally ill who have had to depend upon society for their care with indifference, neglect, and hostility.

Although there have always been a valiant few professional and lay persons who remembered and cared for the mentally ill, our public attitudes in general have resulted in their being kept out of sight, feared, and shamefully neglected. Some of us can even, God help us, recall hearing the belief expressed that the mentally ill were being justly punished for their sins.

Underlying all these attitudes, the enlightened and unenlightened alike, was a pervasive hopelessness so deep that sensitive and well-meaning citizens could stand to look at the problems of the mentally ill only intermittently. Though victims of these diseases have been known to recover in all periods of history and in most societies, the etiology of most mental disorders has been unknown and we have not, until very recently, known how to bring them under control.

Today the occurrence of a mental disease can still be, and in many cases still is, a tragedy not only for those who suffer from the disorder but also for their families and friends. But in the tragic aspect of these disorders is giving way to increasing hopefulness. And since we can now look forward with well-founded confidence to the time when these diseases will be brought under control, and when most of the sufferers assuredly will be socially restored, we can expect our public awareness to remain constant and open.

A little later on I would like to review for you a few of the medical, scientific, and social developments that have led to this increased hopefulness.

At the moment, however, I would like to develop this theme of public awareness a little more fully. I can say with confidence that the needs of the mentally ill shall remain in public view. At the close of World War II, besides the mentally ill themselves and their families, only a few thousand professional persons and a handful of dedicated citizens knew, or cared, what was happening inside the walls of our massive State hospitals. Today these few have been joined by thousands of colleagues and tens of thousands of friends.

Public concern for these problems can be measured in any number of ways: in the number of new clips about mental health appearing in newspapers all over the country; in the increasing number of published books, pamphlets, and scientific papers concerned with these problems.

There are other indexes. Fifteen years ago, public health officers and other health and welfare personnel functioning on the local levels of government felt that the problems of the severely mentally ill were not a concern of "public health" as they defined that term. Only in the 1950's did progress in this field justify a section on mental health in the American Public Health Association, and only in this past year has the APHA been able to prepare a "Guide To Control Methods for Mental Disorders" and publish a guide to "Community Resources for Emotionally Disturbed Children."

As another index of wider professional concern about these problems, the American Medical Association this past fall held a 3-day national working conference devoted to the problems of the mentally ill and mental illness. The AMA now plans to sponsor a series of congresses on mental health and illness to work out a program in which the physician can both assume leadership in areas of his competence and work collaboratively with all professions and agencies that relate to this vast field.

Beginning with the passage of the National Mental Health Act, congressional interest in, and notable support of, mental health activities has been a key factor in the increasing concern at all levels of government in these problems. Two recent concrete measures of this political interest were the special Governors' Conference on Mental Health held in November, at which the Governors adopted a policy statement delineating what a balanced State program for mental health should include, and the appointment by the President of a special panel to study the needs of mentally retarded persons.

Much of this increased public awareness has been stimulated by the work of the Joint Commission on Mental Illness and Health, which was made possible by congressional action and support. In particular the Commission's transmittal to you, and the subsequent publication of their final report has made the public acutely conscious of the need for action.

We at the National Institute of Mental Health are following this reaction with interest, and participating in it to the degree and in the manner appropriate to our role as the primary agency of the Federal Government concerned with mental health.

There is one further reason why I can say that the mentally ill of this country shall not be forgotten nor neglected from now forward. I believe there can be few snakepits in a country where tens of thousand of its citizens care enough about the mentally ill to work, as volunteers, in schools for the retarded and hospitals for the mentally ill.

These volunteers, of all ages, from Cub and Brownie Scouts to members of the Golden Age groups, know, from these experiences, something of what goes on in a mental hospital. They know that the severely mentally ill are not a different order of human beings but our fellows, needing expert and compassionate care. And upon this leaven of the personal involvement of ordinary citizens in the fate and in the care of mentally ill persons unrelated to them, we have a source of support of unusual strength.

At the conclusion of World War II, these allies were few indeed. Dr. Karl Menninger, summarizing the attitude of "Mr. Average Citizens" in his introduction to Albert Deutsch's crusading book, "The Shame of the States," said:

"The average citizen of this country rests in oblivious peace because * * * he knows so little about mental illness he can shut it out of his mind. * * * When Mr. Average Citizen visits (a mental hospital) and observes that the patients therein do not correspond to his conceptions of insensibility and bereftness * * * he is bewildered; he is more than a little troubled, but he feels helpless. * * * It never occurs to Mr. Average Citizen that these dazed, heartbroken patients would ever be mistreated or neglected. It never occurs to him that for many of them no treatment program whatever exists."

What Albert Deutsch saw when he, and the citizens who followed him, went into the public mental hospitals, is described in this book. I can think of no more dramatic way of indicating to you how much we have changed than by recalling some of these scenes for you. While some could be used to illustrate conditions in a few of our hospitals today, it is one of the joys of my life to realize that these condtions are now the exception, not the rule.

These, then, are some of the things Albert Deutsch saw in the hospitals he visited:

"The male * * * ward was like a scene out of Dante's 'Inferno' * * * winter or summer, these creatures never were given any clothing at all. * * *"

"Beds * * * were packed so tight that patients had to crawl over the foot of the bed to out out. * * * Many had no pillowcases or sheets, sleeping on dirty mattresses. * * * The ward toilet served aso as a pantry and dishwashing stand."

"* * * hundreds of mental patients like these were huddled on benches that lined the black walls or lay on the dirty pallets strewn on the rotting wooden floors."

"There was but 1 attendant to take care of the 139 mentally defective children aged 5 to 12 on this ward. * * *"

Such was a crusading journalist's view of "The Shame of the States." The objectivity of his viewpoint was confirmed by the psychiatric profession which, in 1946, through the American Psychiatric Association, began to provide for the inspection and rating of all mental hospitals, and to bring to the attention of all State authorities deficiencies requiring correction. At approximately the same time, the newly organized group for the advancement of psychiatry cited such facts as the following as demonstrating the need for such action:

> Patients are treated in institutions at a cost as little as 43 cents per patient day.
>
> Many mental patients throughout the country were still confined in jails for lack of beds in overcrowded hospitals.
>
> In one State hospital, one full-time and one half-time doctor were taking care of nearly 1,100 patients.
>
> In another State hospital a single nurse had to take care of 1,320 patients.

With the true situation concerning the plight of our mentally ill well documented, and with a dedicated group of professionals bent upon reform, the action of Congress in passing the National Mental Health Act in 1946 marked the beginning of a new age for the mentally ill and of mental health.

In the years since then, the Institute has made significant progress toward solving the problems for which it was established. It has assisted State and local governments provide for extramural facilities for the care of the mentally ill. It has provided for the training of mental health professionals. And it has stimulated, aided, and conducted research in the cause, prevention, and treatment of the mental disorders. We have, in short, made a contribution to the new age for the mentally ill.

We have not, however, been alone in our efforts. In all the States, legislators and professional workers and private citizens have labored steadily, year by year, to correct the conditions so shockingly revealed in the press and in public testimony in the late 1940's. And though the "Final Report of the Joint Commission on Mental Illness and Health" has made it clear beyond question that the uncompleted tasks ahead are fully as difficult as any yet faced, we have made considerable progress. Furthermore, much of this progress has been accomplished in ways that were not foreseen at the time of the great awakening of our public conscience, and with tools and techniques that were not then known or invented.

In the late 1940's, the greatest nightmare of the mental hospital superintendent was the year-by-year increase in the number of patients who were resident in public mental hospitals. Each year, more beds were crowded into corridors. Each year already overburdened facilities were called upon to care for more and more patients. This situation is now changing. In 1948, 323 persons out of every 100,000 persons in the country were patients resident in a public mental hospital. By 1960, this rate had decreased until only 305 persons out of every 100,000 were resident in such hospitals, a decrease of 18 per 100,000.

Other nightmares were insufficient personnel and inadequate funds for the proper maintenance of patients. Even today, little progress has been made. In 1949, the average expenditure per patient day was $1.72 approximately 12 percent of what it cost to support a patient for a day in a general hospital. In 1960, the average expenditure per patient day was $4.72, about 15 percent of the costs for a day of general hospital care. And, in our public mental hospitals, we are still seriously short of all categories of personnel.

However, quite apart from such quantitative measures as resident patient rates, maintenance expenditures, and ratios of personnel to patients, the greatest improvement has been in the atmosphere of our public hospitals. With the discovery, in the mid-1950's, of the usefulness of the psychoactive drugs in controlling the symptoms of mental illnesses, came the hope and belief that it would become possible, sometime in the future, to convert our "snakepits" and "human warehouses" into true hospitals.

The results of the first use of the psychoactive drugs at Rockland State Hospital in New York and Modesto State Hospital in California were reported in February and October of 1954, at a New York Academy of Sciences symposium and in the Journal of the American Medical Association. The JAMA article states in part:

"'For this investigation we have selected only those patients who had the worst prognosis as far as recovery was concerned. They were the so-called back ward patients who had been regarded as hopeless * * *. Prior to this study, these wards presented the usual picture of wards of this type; namely, 10 to 12 patients in seclusion, some also in camisole or other types of restraint. In addition, heavy sedation and electroconvulsive therapy, as well as hydrotherapy and wet packs, were necessary and being utilized daily. * * *

"Since the advent of therapy * * * changes in the patients' attitudes and behavior have been noted. * * * Patients have undergone a metamorphosis from raging, combative, unsociable persons to cooperative, friendly, relatively quiet persons who are amenable to psychotherapy and rehabilitative measures. * * * At present * * * seclusion, restraint of all types, sedation, and electroconvulsive therapy have been almost eliminated. * * * We expect it to revolutionize and facilitate modern psychiatric treatment."

Though the psychoactive drugs do not, so far as we know, "cure" patients, and though we do not yet know the cause—or cure—of the major psychosis—it is now possible, as it was not in the late 1940's to control the symptoms of the major psychoses, and to restore to a socially useful life in the community many more of the mentally ill.

This possibility has touched off the most exciting and promising development in the entire history of the care and treatment of the mentally ill. I am referring now to the whole new series of concepts and services that may be grouped together under the term "community psychiatry." The term includes such concepts as the day and the night hospital; it includes the "open" hospital concept, concepts concerned with "milieu" therapy. It includes such services as emergency psychiatric service, after-care services, outpatient services, and a host of other developments.

It is through the development of these concepts that a new age for the mentally ill and of mental health is coming into being. For example, in 1947, we had only 471 outpatient psychiatric clinics. By 1960, this number had grown to 1,505.

Other increases confirm the dramatic growth suggested by these figures. Between 1956 and 1960 there was a more than fourfold increase in expenditures for community mental health programs throughout the country.

In 1961, total Federal, State, and local funds budgeted in State plans for community mental health programs amounted to $91 million. The latter figure included Federal funds amounting to $6 million. Ten years ago, Federal funds accounted for 27 percent of the total budgeted funds.

I suggested, early in my statement, that the ferment, the activity, and the determination to bring about changes that have characterized our field in the last 15 years is equivalent to the type of activity that has, in the past, signified the beginnings of remarkable developments in man's history.

DEVELOPMENT IN COMMUNITY SERVICES AND HOSPITALS

I wish to emphasize that statement, and to mention a few of the hundreds of reports we have received at the Institute in the past year that confirm this belief.

The Council of State Governments reported this fall that increases in State expenditures for community mental health programs have been impressive. In about one-half of the States, increases in funds budgeted for these purposes ranged from 30 to 100 percent between 1961 and 1962. In Connecticut the first of a series of small, community-based mental hospitals was being built. Minnesota reported that it now had 14 mental health centers accessible to 48 percent of the State's population. New York indicated it had increased the number of outpatient psychiatric clinics in the State from 142 in 1959 to 167 in 1962.

In Nevada, Maine, Ohio, and North Carolina, commitment laws were revised to permit admission of a patient to a mental hospital on an emergency, or voluntary basis.

In Nebraska, it was found that 60 to 90 days of inpatient care, followed by day-patient care over a period of 1 or 2 years, can in many cases help a severely ill child as much as 1 or 2 years of inpatient treatment.

In New Jersey a new demonstration project for the treatment of juvenile delinquents was started. First offenders were "committed" to a day center where they received work training, group therapy sessions, and where they were given an opportunity to enjoy wholesome recreation.

In California, an alcoholism clinic reported that in the 2½ years since the clinic had been operating police bookings on drunk charges, and reports of delirium tremens cases had decreased by 50 percent.

Emergency psychiatric treatment services of various kinds, including "drop-in" clinics and home visits, were reported to be operating in Berkeley, Calif., Suffolk County and Brooklyn, N.Y.; Washington, D.C.; Providence, R.I., Philadelphia, and Boston. The home treatment service in Boston, operating out of Boston State Hospital, reported that they had found that 60 percent of the persons referred for hospitalization could be treated without admission to the hospital by an effective home treatment team.

In Georgia, the State reimbursed four general hospitals for the care of psychiatric patients who would otherwise have been admitted to the State hospital. Six hundred and fifty patients were treated in this way, and, after an average length of stay of only 23.4 days, between 80 and 90 percent were discharged to their communities.

The problem of whether or not it is feasible to include office visits to a psychiatrist in a group health insurance program was investigated in New York City. Reports from this demonstration project indicated that "short-term ambulatory and hospitalized psychiatric treatment may well be insurable for the average subscriber already covered in a comprehensive group insurance program."

Projects devoted to caring for the mentally retarded in the community were reported from several States. In Rhode Island, an information, consultation, and referral center made possible by a private donor was established to help the families of the mentally retarded obtain the kind of services they need. Working also with social and health agencies, the information center will try to identify unmet needs in this area and, through community planning, work toward meeting these needs. A program to determine whether comprehensive community care could prevent the hospitalization of mentally retarded infants was started at Flower-Fifth Avenue Hospital. In California, the State department of mental hygiene attempted to find suitable alternatives to State hospitalization for the 1,600 mentally retarded on the waiting lists of the State schools. Under this program, operators of private psychiatric facilities were subsidized for caring for State patients, some of the mentally retarded persons were placed in family care, and three diagnostic, evaluation, and placement centers sought to cut down on the number of mentally retarded who would not be cared for anywhere except in the State schools.

Care of the mentally ill within the State mental hospitals continued to improve. In Arkansas and New York, between 65 and 70 percent of the wards were "open" wards. South Carolina reported between 75 and 80 percent of all the wards were open, and Kentucky reported that it had two completely "open" hospitals.

Discharge rates continued to improve throughout the country. In Kentucky, 72 percent of all patients admitted to a State hospital for the first time was discharged within 3 months, and 95 percent were discharged within 11 months. Other States submitted comparable reports: In Georgia, 70 percent of first admissions were discharged within 3 months; in Connecticut, 80 percent within 3 months; in the State of Washington 85 percent within 12 months.

DEVELOPMENTS IN TRAINING

As the State mental hospitals seek to become more effective, some steps are being taken to improve the quality of personnel serving in mental hospitals by providing for inservice and on-the-job training. Not all forms of training are available at every institution or even in every State, but there is hardly an institution that does not offer at least some inservice training, upon which much more effective programs can be developed, to many types of ancillary personnel, especially aids and attendants. The States are also establishing stipend programs in an effort to recruit, train, and retain well-qualified personnel, as well as to give promising employees a chance for advanced training qualifying them for higher positions.

Through a grant awarded by the Institute to the Western Interstate Commission for Higher Education, a 3-year project will promote programs of inservice training for staffs of western public mental hospitals and schools for the retarded. In West Virginia, a training center for psychiatric nurses has been established at Huntington State Hospital. In California, selected psychiatric technicians may enter a 2-year nursing program in a junior college to become qualified as registered nurses.

The importance of providing young psychiatrists with skills enabling them to work in community mental health programs has been recognized in a number of States. In Maryland, third year psychiatric residents spend some time each month working county health units on community mental health programs.

Institute graduate training grants supported 2,526 trainees in 1960. Of appointments made in the mental health disciplines, 26 percent were for regular graduate training in psychiatry, 18 percent were in clinical psychology, 26 percent were in psychiatric social work, and 11 percent were in graduate psychiatric nursing. Other training areas for which appointments were made were psychiatric residency training for general practitioners; psychology, other than clinical; social work, other than psychiatric; public health (for mental health professions), the mental health aspects of the biological sciences and the social sciences; and certain special programs, for example, juvenile delinquency and mental retardation.

The number of Institute-supported postgraduate courses designed to improve the psychiatric skills of nonpsychiatric physicians continued to increase. During the first academic year that funds were available for this program, the NIMH granted at least partial support to a total of 25 courses; by last year the number had risen to 50. It is estimated that several hundred physicians are reached each year by Institute-supported or similar courses.

DEVELOPMENTS IN RESEARCH

In addition to service and training activities, increased attention was being given to research by State mental health programs. In California, the 1962–63 budget for research was six times as large as it had been in 1957–58. New Jersey increased appropriations for research by 160 percent in 2 years. Even though many States do not have a special budget for research, many of the hospitals and some of the central offices provide or or are planning to provide for a position of director or coordinator of research. This is the case, among others, in Kansas, Kentucky, Missouri, South Carolina, and Connecticut.

At the National Institute of Mental Health this year, grants designed to give impetus to the development of broadly conceived centers for clinical research and programs were awarded for the first time. Grants were awarded to the Research Center for Early Childhood Schizophrenia at the Indiana University School of Medicine; a research center focusing on mental retardation at the University of Nebraska School of Medicine; a psychiatric research center for the study of the psychoses, at the Massachusetts Mental Health Center, Boston; and a center for psychosomatic and psychiatric research at Michael Reese Hospital and Medical Center, Chicago. In addition, grants were awarded to establish a psychobiological research program at the Johns Hopkins Hospital and Medical School, Baltimore: a psychiatric treatment research center and program at the State University of New York, Downstate Medical Center, New York; and the Center of Alcohol Studies at Rutgers, the State University in New Brunswick, N.J.

Some of the results of the various research efforts conducted or supported by the Institute are available in the document entitled "Highlights of Progress in Mental Health Research, 1961," which you have already received.

In general, scientists from an increasingly large number of disciplines utilizing an ever wider range of approaches are investigating the various aspects of mental illness. Because an important discovery may be made through any one of these disciplines, every possible approach that may shed light on the many factors related to mental illness is being utilized.

While the sum of these researches constitutes a very complex and interrelated pattern of attack on the problem, current research can be divided into the following four major areas: (1) Studies dealing with the biological factors associated with mental illness; (2) investigations concerned with the whole spectrum of normal and abnormal processes of development; (3) studies focusing on the social and epidemiological factors relevant to mental disorder; and (4) projects of relevance to psychopathology, diagnosis, and treatment of mental diseases including basic studies in psychological and behavioral sciences.

The central goal of the biological research is to understand how certain physiological functions of the body are related to emotional and intellectual behavior. Knowledge now accumulating from work in the biological sciences—

for example, in genetics, in the anatomy and physiology of substructures of the brain, and in central nervous system biochemistry—may, in time, help identify important physiological differences between the normal and mentally ill individual. Investigators are attempting to characterize specific biological functions associated with such disorders as schizophrenia, mental retardation, alcoholism, and drug addiction. From their findings, it is hoped will come knowledge useful for the development of methods of prevention and treatment of these afflictions.

Such have been some of the developments during the past year in our continuing national effort to improve the care and treatment of the mentally ill, and to increase our knowledge about the mental disorders.

TASKS FOR THE COMING DECADE

I would like now to indicate to you, briefly, what we consider to be the major tasks of the coming decade in this field, and to suggest some of the approaches we hope to make in accomplishing them.

ATTITUDES AND INFORMATION

The first task we would hope to undertake would be to assist citizens throughout the country in understanding the mental illnesses, and in developing constructive ways of dealing with the manifestations of these disorders wherever, during the course of their daily lives, they encounter them. We would hope that within a decade, our fellow citizens would have supplanted attitudes of indifference and neglect toward the mentally ill with attitudes providing positive support for and enlightened understanding of what can be done for the mentally ill by new techniques and patterns of care.

We would also hope that, by disseminating helpful and accurate information concerning the nature, cause, and proper treatment of the various mental disorders, we would assist the families and friends of the mentally ill to deal with the manifestations of mental illness not only with compassion but also intelligently and effectively. In addition, we will share with all citizens everywhere whatever we know and learn of ways to prevent the occurrence of the mental disorders.

EPIDEMIOLOGY

Second, in the next decade, we plan to complete the basic, fundamental task of providing a sound body of knowledge concerning the epidemiology of the mental disorders. Such knowledge should include: (*a*) where these disorders exist in population groups; (*b*) what biological, social, cultural, and environmental factors appear to be, or are, associated with these disorders. This type of knowledge will enable us to identify the various groups of people whose vulnerabilities to one or another of the mental disorders are great, and to identify stress factors that are related to the occurrence of psychiatric disorders in various population groups.

Finally, using such basic knowledge, we expect to increase our ability to determine what types of psychiatric services are needed by population groups; in addition we expect to learn what types of assistance the mental health professions can give to the social and health agencies and institutions of a community in dealing with the problems in which the mental disorders play a part, and in meeting the basic mental health needs of our people.

MANPOWER

Our third task, in the next 10 years, will be to continue and to increase our efforts to provide training in the mental health professions and in the allied scientific disciplines to persons interested in a career in the mental health field; to increase the degree and the extent to which mental health skills are available not only to hospitals and clinics but also to schools, social agencies, courts, and other agencies; and to provide appropriate mental health skills and knowledge to key persons in the community, such as nonpsychiatric physicians, clergymen, and lawyers.

Since realistic estimates of our future needs for mental health personnel and for other professional persons with mental health and scientific skills indicate that we shall be hard pressed adequately to meet the needs for service, training, and research, a part of our efforts will be devoted to determining in what ways psychiatric, scientific, and mental health skills may be most effectively utilized.

RESEARCH

We see our task in the research field in the next decade to be similar to those we have undertaken in the past 15 years. However, unlike our situation just after World War II, we now have, in the Nation, a research potential of considerable effectiveness, and a growing body of skilled researchers. Over the years, we have vastly extended the areas in which productive research can be performed, and we have added a whole new group of disciplines, including the behavioral sciences, to our research efforts.

We would expect, in the next decade, to continue to investigate clues leading to an understanding of the etiology of the mental disorders, to try to develop effective methods and techniques of treatment, and to discover ways of preventing these conditions. Since our growing research potential now makes it appropriate to conduct long-term and basic research to a greater degree than was appropriate 10 and 15 years ago, we expect that our grant-supported and intramural research program will be, to an increasing degree, devoted to this type of research. However, we have in the past, and continue still, to believe that our research portfolio should be balanced between applied and basic research, and short-term and long-term projects. In our efforts to understand the problems of adaptation and maladaptation, we will continue to pursue knowledge which will shed light on man as a biological organism and as a social creature.

SERVICES FOR THE MENTALLY ILL AND THE PROMOTION OF MENTAL HEALTH

We believe that one of our major tasks in the next 10 years will be to stimulate the full application, on a State and local level, of all the knowledge we now have concerning the most appropriate and effective ways of dealing with the mental disorders, both acute and severe, chronic and disabling.

We recognize that the full application of our present knowledge may well lead, in the next decade, to a major realinement of facilities and programs providing services to the mentally ill. We expect that, if present trends in the development of services and programs continue and are accelerated, in 10 years the great majority of mentally ill persons in the country will have effective treatment facilities available to them in their own communities. Furthermore, we believe that to a much larger extent than is now possible, persons in the nonclinical or early clinical stages of their illnesses will receive help designed to minimize or to prevent the development of a disabling mental disorder.

Since the realinement of these service programs and facilities will be in the nature of a major national undertaking, we will hope and expect to conduct appropriate operations research to evaluate the presently emerging patterns of services and programs.

AREAS OF SPECIAL NEEDS

In a complex and changing society such as ours, special and unforeseeable problems can develop with surprising rapidity. I am thinking now not of such foreseeable problems as those resulting from the fact that we can expect our population, in 10 years' time, to include a larger proportion of young adults and aged persons. I am thinking, rather, of special stresses such as those experienced by people and groups as they attempt to adapt to a changing environment. The extent to which the United States is becoming urbanized is one such factor, as is the increasing mobility of our population.

If we are to continue to be truly a National Institute of Mental Health, these special areas of need must be anticipated and planned for.

CONCLUSION

I suggested at the beginning of this statement that we are experiencing, in the field of the mental disorders, a period of turmoil, creativity, and experimentation. I suggested further, that as this period progresses, we may be witnessing the first stages of developments that may appear, in retrospect, to have been truly momentous in their effect upon our knowledge of, and the way we deal with, the mental disorders. Further, I do not consider it inconceivable that the effect of the work undertaken by the Institute in the coming years will be even more significant. As we struggle to comprehend and deal with these baffling and complex disorders, we are inevitably increasing our understanding of human nature and of man. And as we take small steps, day by day, to increase our intellectual mastery over human phenomena, we may be approaching the time not only of a major breakthrough in our understanding of the mental disorders, but also of a major breakthrough in our understanding of man. If this be so, we might then be able to seek a solution, with rational knowledge and scientific skill, to meet the needs of men to learn how to become more constructively adaptive as individuals in an increasingly complex and competitive society.

I would like to close this portion of my statement by repeating an observation made by Raymond Fosdick at the dedication of the 200-inch telescope on Mount Palomar in 1948, when those present were allowed to look at a star never seen by man before. Mr. Fosdick reminded his audience that although the philosopher may say, "Astronomically speaking, man is completely negligible," the psychologist can reply, "Astronomically speaking, man is the astronomer." We would endeavor, in the coming years, to comprehend the truth of this response.

The request for 1963 is $126,899,000 as compared to an operating level in 1962 of $103,449,000 and an appropriation of $108,876,000. This allowance in 1963 will provide for the continuation of 1962 program levels in all activities. The increase of $23,450,000 will provide increases in research grants and training grants; in direct research it will provide for expanded activities in research on schizophrenia, neural anatomy, biosocial growth studies, clinical science, neuropharmacology, statistical processing of research data, and renovations in laboratories at the Addiction Research Center and the Clinical Neuropharmacology Research Center; in collaborative studies, for more extensive biometrics research and community research; in training activities, for the second phase of the career development program; in the review and approval of grants, and administration activities, the increases will provide staff expansion, to better service and direct the Institute programs.

The request for 1963 is distributed among program activities as follows:

Grants and related contracts:	
Research	$54, 437, 000
Fellowships	2, 892, 000
Training	44, 650, 000
State control programs	6, 750, 000
Subtotal, grants and related contracts	108, 729, 000
Direct operations:	
Research	9, 775, 000
Collaborative studies	2, 573, 000
Training activities	596, 000
Professional and technical assistance	2, 122, 000
Review and approval of grants	2, 413, 000
Administration	691, 000
Subtotal, direct operations	18, 170, 000
Total 1963 appropriation request	126, 899, 000

DECREASE IN NUMBER OF MENTAL PATIENTS

Dr. Felix. It is with a great deal of pleasure, sir, that I report that for the sixth consecutive year now the number of patients in public mental hospitals has declined. The number of patients at the end of of 1961 was 526,414. This is a little over 9,000 less than at the end of 1960—about 1.7 percent less.

You might be interested to know also that this is over 100,000 less than the number that was projected in 1955 on the basis of an 11-year experience, about 17 percent less than we would have expected on the trend of the 11 years before that.

In addition to this, there are some other interesting trends in this direction. New York State has done a study recently and reports that their schizophrenic patients who have been hospitalized for 5 years or more—which constitute the hard core of the hospital patient problem——

Mr. Fogarty. Is this the Rockland Hospital you are talking about?

Dr. Felix. This is the whole New York State system, yes, those hospitals under the jurisdiction of the department of mental hygiene. Those patients who have been hospitalized for 5 years or more have dropped 20 percent over the last 5 years—these schizophrenic patients who have been in for this length of time.

You may remember that in years past we have stated that schizophrenic patients who have been hospitalized for 5 years or more had a smaller chance than 1 in 100 of getting out alive. This trend is now being reversed.

Mr. Fogarty. The schizophrenics make up more than half of the mentally ill; don't they?

Dr. Felix. That is correct; more than half of the mentally ill hospitalized on any day. They are the big burden on the taxpayer because of the number in hospitals.

COMMUNITY MENTAL HEALTH LEGISLATION

Some of the reasons back of this, I think, would be appropriate here. Four more States this year have passed community mental health legislation. This is legislation which authorizes the State to share with localities in financing community mental health facilities.

There are now 13 of these States: Oregon, South Carolina, Utah, and Wyoming this year; New York in 1954; Indiana, Connecticut, in 1955; New Jersey, Minnesota, and Vermont in 1957; Maine, South Dakota, and Wisconsin in 1959.

Other States have adopted a slightly different plan. Kansas and Iowa have a plan in which they have authorized their counties to levy a mill tax—in the case of Kansas, not to exceed one-half mill—which is to set up community mental health facilities. The State assists by giving consultation and loaning personnel.

In the case of Iowa they have now set up 12 community mental health clinics like this; and on the basis of their local taxation are expending—based on 1961 experience—a little over $600,000 a year for this purpose.

MENTAL HEALTH CLINICS

Now, as a result of this kind of activity, mental health clinics in the country are increasing in number. The last full year for complete data was 1959, with 1,429 mental health clinics in the United States. Of these, 39 were special clinics for alcoholics. There are about 80 special clinics for the retarded, in addition to some general psychiatric clinics which are treating and assisting with this problem.

Of these 80, I think you should know that 50 are supported by the Children's Bureau under their budget. Minnesota is employing family group therapy, which has always before been a hospital type of procedure, in their clinics, and with considerable success.

HEALTH INSURANCE

Another reflection of the change in attitude has been what is occurring in the area of health insurance for the mentally ill. The trend is toward expanded insurance coverage for these people. Fifty-eight of the eighty-three Blue Cross plans in the United States now provide 21 days of care in their benefit period for psychiatric care, although only 13 of these Blue Cross plans offer coverage for the mental disorders to the same extent that they offer it for most physical illnesses.

In California, another interesting development in this line: The Retail Clerks Union No. 1770 has instituted psychiatric coverage for all of their 30,000 subscribers and their families. That is part of their total health plan.

The report is that this is not going to require additional subsidies of any kind, but can be covered under their regular insurance plan.

AGING

In the field of aging, there are a number of interesting developments. A nurses' home in a hospital near Harrisburg, Pa., has been converted into a mental health center for aging people. Louisiana has developed a geriatric hospital for nonpsychotic patients who have nowhere to go, the homeless old people. New York City has provided psychiatric consultation service for programs serving the aged. They service about 13 institutions.

ALCOHOLISM

In the field of alcoholism, New York State has set up a division of alcoholism in the department of mental hygiene. Kentucky has established a division of alcoholism. Iowa has created a division of alcoholism. West Virginia has converted a State hospital to a treatment center for alcoholics.

Florida has a new program for treating alcoholic probationers and parolees which looks very interesting. In San Francisco, they have established what they call a quarter house, as opposed to a halfway house for men released from jail who were alcoholics.

Mr. FOGARTY. What is a quarter house?

Dr. FELIX. They give them 2 weeks living away from skid row after they have been released from jail. These are skid row people. And they are near employment centers. They give them a small allowance for necessities and assist them in getting jobs.

As you know, one of the problems with the skid row people is that nobody will accept them once they get that far down. This gives them the chance to come back and rehabilitate themselves.

MENTAL RETARDATION

In the field of mental retardation the New York Medical College is developing with our support an experimental program to study the effects of comprehensive medical care on young retardates less than 5 years of age who have been on a waiting list for institutions.

Illinois has developed a new training and research center for the training of people to work with the retarded. Indiana plans a research hospital on retardation on the University of Indiana campus.

I might say there are two very interesting developments in Indiana. At the University of Indiana they are now developing an experimental program on machine training in the teaching of reading, the so-called automated teaching of reading, which is a very exciting new development in the whole field of education.

At the Muscatatuck State School at Butlerville, Ind., they are using this automated teaching for the teaching of arithmetic to retardates. They are pleasantly surprised at the success they are having with it.

Ohio now has community classes for retarded youths, and the State is financing sheltered workshops and classes. There are about 250 of them in 1961. Minnesota has community day-care centers for the retarded. Pennsylvania has a counseling service for them and their families.

RHODE ISLAND PROGRAM

In Rhode Island there has been appointed a special study commission for this. The most interesting thing in Rhode Island is a demonstration of statewide services of counseling and referral, which is jointly sponsored by the State council on community services and the State association for the mentally retarded.

This was initiated by a gift of a very prominent Rhode Island citizen. He is the Honorable John E. Fogarty, of Rhode Island, who very magnanimously gave as an initial gift an award of significant size that he received. I believe it was the Lasker Award. We have now entered into this and are assisting it to a significant degree and plan to do so for some time in the future.

This was so exciting that we were most anxious to get into this, and have done so. We wanted to assist this.

They are dealing with families of the retarded as well as the retarded themselves. They are counseling with them and helping them to understand what facilities there are in the Rhode Island area for assisting these children and these people after they have had what assistance they can get through classes and so forth.

They are giving the parents insight into both what they can expect and what they cannot realistically expect in terms of their child and its development.

Mr. FOGARTY. Isn't it also being used to prepare expectant mothers regarding this problem, if it should happen?

Dr. FELIX. That is correct. They are also using it for counseling and preparing expectant mothers so they will know what to expect if this happens and what they can do about it.

Mr. FOGARTY. Many of them have ended up in institutions, haven't they, when it has happened?

Dr. FELIX. That is correct. The shock has been just more than they can handle. It all boils down to the fact that, as someone recently said, the retarded has every right to all of the privileges that any other human being and any other citizen would have within his capacity to handle those privileges of our society.

We are more and more amazed at how many of these privileges they can enjoy if they have the proper training early enough and if the family knows what to expect and how they can work with them.

EMERGENCY PSYCHIATRIC SERVICE

In the field of emergency psychiatric services here in Washington, D.C., the Health Department has set up a panel of private psychiatrists who make home visits to financially needy families where there is a problem that they may be able to handle in the home rather than in the hospital.

A similar program is going on in Suffolk County, N.Y.

PSYCHIATRIC SERVICES IN GENERAL HOSPITALS

In the area of psychiatric services in general hospitals, the Veterans' Administration is constructing a general hospital in the Washington area. It will be the new Mount Alto Hospital. It is a 710-bed hospital, which will have 240 beds for psychiatric patients. They will accommodate both acute and chronic patients. They will be handled as any other hospital patient.

The Veterans' Administration is now planning in all of their current general hospitals to provide psychiatric care for patients as well as other types of care.

In Illinois $750,000 of State aid money is now going for the care of psychiatric patients in general hospitals. In New York and California and Connecticut they make extensive grants to localities for psychiatric care in general hosiptals.

In Iowa and Tennessee and in Texas they are emphasizing this more and more. More and more patients are being treated in this way. Also in Georgia.

DAY HOSPITAL

Day hospitals are growing in popularity. They have them now in Oregon, Texas, New York, Kansas, Iowa, Nebraska, and California that I know of for sure; and I think there are other places.

Mr. **Fogarty.** And Rhode Island.

Dr. **Felix.** And Rhode Island, yes, sir. I beg your pardon; that is true. This is true in Rhode Island, I believe both at the State Institution and at the Butler Health Center. I forgot that; I am sorry.

Mr. **Laird.** You should be.

Dr. **Felix.** Yes, sir, I should be—for another reason than what you think, Mr. Laird. I have visited it several times and I know it from personal contacts. So I am embarrassed as well as chagrined.

INCREASE IN VOLUNTARY ADMISSIONS

The admissions to mental hospitals more and more are becoming a matter of voluntary admissions. The proportion of voluntary admissions in State hospitals is going up. In 18 States we have studied recently, 26 percent of all admissions to the public mental hospitals were voluntary.

They are, as I have said, developing these comprehensive mental health centers in various parts of the country. Illinois has just approved a bond issue to construct six of these, which will include 160 beds for all types of mental illness, including the aged, alcoholic, retarded, emotionally disturbed children, as well as adequate outpatient and rehabilitative services.

OPEN HOSPITALS

Open hospitals are increasing. In Kentucky they have two hospitals that are now completely open.

Mr. **Fogarty.** What do you mean by "open hospitals"?

Dr. **Felix.** No locked doors in the hospital. The whole hospital is open. Patients come in and they go out. They can now be controlled as far as unfortunate behavior is concerned by a wide variety of drugs which will make them more tranquil and more amenable to care and treatment.

There is no need to lock them in any more. We have known for years that locking a patient up was in and of itself a deleterious type of activity—as it would be for any of us if we were rushed into a hospital and the door locked behind us and we were divested of our usual clothing and our watches, rings, keys and so forth and then were locked in. We would feel completely at the mercy of the staff.

This in itself throws a barrier across the road to best possible recovery.

As I say, in Kentucky two of their hospitals don't have a locked ward door in them. In Minnesota the Wilman Hospital is fully open. In New York they have a hospital completely open at Syracuse; and in the entire State of New York, 69 percent of the patients in the hospitals under the supervision of the department of mental hygiene are in open hospitals.

AFTER-CARE AND REHABILITATION SERVICES

They also have open hospitals to a significant degree in Arkansas, South Carolina, Tennessee, and Connecticut.

After-care and rehabilitation services are increasing. Georgia and Alabama are using this extensively. Texas is now using it. In Washington State they have nursing home placement teams in each of the State hospitals. In Michigan they have a consultation center in Detroit which is operated by the department of mental health. It provides free admission and followup services in the State.

California has about 1,500 patients now in foster home care programs. New York, Maryland, Ohio, Indiana, and Missouri all have large and growing foster care programs.

EMOTIONALLY DISTURBED CHILDREN

One area that is still a matter of concern to us is the area of the emotionally disturbed child. This is not yet being adequately met. We are working hard on this. There are some 11,500 children admitted to public mental hospitals each year.

Mr. **Fogarty.** Do you have a definition of an emotionally disturbed child?

Dr. **Felix.** These are usually psychotic children, or children sufficiently mentally ill, even though they may not be psychotic, so that they cannot be in the opinion of the authorities, family and all, handled outside of a restricted environment such as an institution.

Mr. **Fogarty.** The Bradley Home is considered a real good institution for emotionally disturbed children, isn't it?

Dr. Felix. This is correct. It has been for many years. It is one of the top-flight institutions. I would put the Bradley Home in the top—I was going to say half-dozen. Let me, just to be sure I am not making it too strong, say the top dozen such places in the United States.

Mr. Fogarty. The last time I visited there it seemed to me they had more people from the State of Connecticut than any other outside State. I was wondering why. Do you know?

Dr. Felix. I don't know. There is a provision, as you know, Mr. Chairman, in the charter—something like Butler Hospital—whereby they must give preference to Rhode Islanders insofar as they are needed. But this takes up only a small portion of their beds.

They did in the days when I was a resident at the Bradley Home come from long distances. We had children from the Midwest.

CHILDREN IN PUBLIC MENTAL HOSPITALS

You will be interested to know, I think—and I suspect somewhat disturbed to know also—that on any day of the year there are about 13,500 children in public mental hospitals. Most of these are mixed in with adults because there is no provision for their special care.

Some States are moving away from this. Indiana has just authorized the creation of five residential treatment centers to treat these children separately. North Carolina has now funds for a treatment center for mentally ill teenagers.

Texas has authorized a 30-bed treatment unit for children with outpatient facilities at the University of Texas Medical Branch. Wisconsin has day-care centers for emotionally handicapped children. There are a number of them authorized.

The prototype was itself one at Madison at the university, which has been running for a number of years with great success.

Tennessee is about to participate with another State yet to be selected on some of these residential treatment centers to bring about this regional concept about which we have talked. With this kind of scarce personnel every State cannot afford such a hospital because they may have a small population or for other reasons. So we are trying to develop these on regional basis where we possibly can.

All of this to me points up the significance and importance of what I think has been the most exciting development during the years that I have been connected with the mental health movement—certainly during the nearly 18 years that I have been Director of the Institute or as Chief of the Division, its predecessor.

FINAL REPORT OF THE JOINT COMMISSION ON MENTAL ILLNESS AND HEALTH

That is the report of the Joint Commission on Mental Illness and Health.

I am particularly interested because of the kind of acceptance this has had and the kind of interest it has stirred up. There was a special Governors' conference called in Chicago to discuss this report. A resolution was unanimously adopted supporting the recommendations of the report and strongly recommending that it be implemented.

Mr. Chairman, if the committee would wish, I have a copy of the report of the Governors' conference which I would be happy to submit for the record.

Mr. FOGARTY. We will put the whole thing in the record, and the resolution which was passed by the Governors' conference in Chicago.

Dr. FELIX. Thank you.

I also have the digest of the final report of the Joint Commission which I can submit.

(The requested information follows:)

POLICY STATEMENT AND RESOLUTIONS[1] ADOPTED BY THE SPECIAL GOVERNORS' CONFERENCE ON MENTAL HEALTH

Chicago, Ill., November 9–10, 1961

For more than a decade, the Governors of the several states have been profoundly concerned over the inadequacy of care and treatment of the mentally ill—still the number one health problem of the nation. Their concern was evidenced not only be requests to the Council of State Governments for comprehensive studies of the mental health programs of the states and of methods for converting their custodial institutions into active treatment facilities, but also by their calling, as a result of these studies, the historic special National Governors' Conference on Mental Health in Detroit, in 1954. A basic Ten Point Program was adopted at that meeting, urging intensification of efforts in the areas of community services, treatment, rehabilitation and aftercare as well as research and training.

The Joint Commission on Mental Illness and Health, pursuant to Congressional authorization, has been studying these problems for the past six years. The Commission's Final Report—Action for Mental Health—is the first survey in our nation's history which relates the problem of mental illness to the various responsibilities of Federal, State and local governments. The Report indicates that progress has been made in the last few years, but leaves no doubt that much too litle has been accomplished. We heartily commend the Joint Commission for an excellent study; we accept the findings that much remains to be done; and we endorse the concept that Federal, State and local government as well as private and voluntary efforts must be combined to achieve the goals we seek.

Approximately half of all hospital beds in the United States still are occupied by patients suffering from emotional disturbances. Many of the state hospitals are seriously overcrowded; about half of their patients receive no more than custodial care rather than active treatment. Financial support has been woefully inadequate and must be increased. Shortage of professional personnel has been the prevailing condition, even when funds are available.

Community mental health services are in such short supply that almost all clinics have waiting lists making it necessary for them to delay services to applicants for periods of from three months to a year. Many states do not appropriate any special funds for research. Aftercare services are lacking in most states. Where they exist, they often are inadequate, leading to avoidable readmission of large numbers of patients to hospitals. Programs of patient care are fragmentary, lacking in continuity and coordination.

In the light of new knowledge and treatment potentials, a balanced state program for the mentally ill should include: Prevention and early case finding and treatment; a complete range of community-based services, emphasizing continuity of treatment; active treatment, rather than custodial care during necessary periods of hospitalization; rehabilitation and aftercare services; specialized services for patients suffering from conditions closely related to mental illness, such as mental retardation, alcoholism, delinquency, drug addiction, deterioration connected with old age, research, recruitment, training, and imaginative utilization of paid staffs and volunteers; effective centralized responsibility for all state-supported services; and involvement of professional associations, and voluntary mental health and social agencies in the basic planning and provision of the highest quality of care for all mental patients.

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[1] Distributed in the Mail Pouch, December 1961, by the American Psychiatric Association, 1700 18th Street NW., Washington 9, D.C. Extra copies available on request.

After careful consideration the Governors' Conference on Mental Health meeting at Chicago, Ill., November 9–10, 1961, recommends that such a program be implemented as follows:

I. COMMUNITY MENTAL HEALTH SERVICES

1. Indications are that 75 percent of the acutely mentally ill who receive intensive treatment in community facilities will not require costly institutionalization. Long-term, costly hospitalization of the mentally ill should be avoided, not only for the sake of economy but also in the best interest of the patient. Whenever possible the patient should be treated in the community, through mental health clinics, emergency and short-term psychiatric services in general hospitals, day and night hospitals, halfway houses, and other rehabilitation facilities.

2. The enactment of community mental health services legislation, under which a State provides matching grants to local communities and nonprofit groups, has served as a stimulus in the development of such services in several states and may serve as an example for others.

II. INPATIENT SERVICES

1. Every American who is suffering from mental illness is entitled to intensive treatment in a facility which is easily accessible to him. Since the so-called chronic mentally ill patient often can be salvaged and returned to the community, any arbitrary distinction between those who suffer from acute mental illness and those suffering from chronic mental illness is to be deplored—all are entitled to the best psychiatric care.

2. This treatment can best be given in small hospitals providing both inpatient and outpatient care in the heart of the community. Programs, therefore, should follow the recommendation of the Joint Commission that smaller hospitals should be constructed and that no beds be added where large facilities exist. Where they do exist, steps should be taken to decentralize them internally into units of appropriate size to ensure the best patient care and maximum efficiency.

3. While for purposes of clarity it has been found expedient to list these recommendations under separate headings, it should be clearly understood that a patient is the same person, whether receiving care in the community or in a hospital, on an inpatient or outpatient basis, and that each treatment facility and medium must be considered an integral part of a continuum of services rendered a patient at various stages of his illness. It therefore is of utmost importance that inpatient services be integrated with community services and that the hospital reach out to the community, particularly to aid in the rehabilitation and aftercare of the patient.

III. PSYCHIATRIC SERVICES IN GENERAL HOSPITALS

The rapid growth of psychiatric services in general hospitals has been encouraging. Because they are expensive to operate in the short run, although cheaper in the long run, it is recommended that states allocate specific appropriations for the support of psychiatric beds in general hospitals.

IV. RESEARCH

1. Research into the causes of mental illness offers hope for its eventual prevention, control, and cure. The states must recognize a responsibility for research and include in their mental health budgets support for substantial research.

2. There is urgent need, moreover, for the various levels of government to apply joint and immediate research efforts toward establishing best possible mental health services in relation to specific population and area requirements on the basis of current knowledge.

3. In addition to government-supported research, a much greater expansion of research activities by nongovernmental groups and organizations is recommended.

V. CLEARINGHOUSE

Planning mental health programs requires information which can be collected and disseminated only by a centralized clearinghouse. It therefore is recommended that the National Institute of Mental Health establish a clearinghouse to supply the states, the local communities, and the general public with mental health information.

VI. PERSONNEL

1. Revised programs for the care and treatment of the mentally ill require review and analysis of staffing of mental health facilities.

2. Review of personnel policies also is recommended for best utilization of available manpower. For example, to enable professionals to devote as much time as possible to their specialties, they should have sufficient assistance to carry on the purely administrative aspects of their duties. Such a policy, at the same time, would offer an opportunity to upgrade the positions of persons qualified to carry out such responsibilities and would serve as a challenge to them.

3. The manpower shortage also can be reduced by—

   (*a*) Provision of more competitive salaries on all levels of employment;

   (*b*) A review of the hospital patient load with a view to alternative disposition of patients inappropriately admitted and retained;

   (*c*) Assistance by the professionals in the recruitment of professional staff for psychiatric facilities;

   (*d*) Reexamination of the qualifications required for service in public mental hospitals.

VII. TRAINING

1. A partial solution to the present shortage of professional manpower lies in better utilization of existing personnel and the addition of substantial numbers of less highly trained staff, intensification of recruitment and training.

2. We must have more people knowledgeable in the techniques of teaching and encouraging mental health and trained in recognizing the symptoms of mental illness.

3. We must lend our efforts to upgrade the counseling skills of teachers, members of the clergy, general practitioners, law enforcement officers, social workers, volunteers, and others.

4. We must educate the public in the nature of mental illness. Consultation with community groups, maximum use of the time of qualified professional people in educating others in the community, and close coordination with mental health associations will bring about community acceptance of mental disorders as illnesses.

5. The states must recognize a responsibility for training and include in their mental health budgets support for substantial training.

VIII. ORGANIZATION OF A STATE'S MENTAL HEALTH ACTIVITIES

It is of utmost importance that all state mental health services—including institutions for mentally ill and retarded adults and children, statewide community services, and training and research—be unified and integrated under responsible, competent, and professional leadership.

IX. ADMISSION PROCEDURES

We recognize no stigma attached to mental illness. The treatment of mental illness should be on the same basis as the treatment of physical illness. A practice of voluntary admission should be encouraged, and it is recommended that there should be movement toward admission without formality, and similar to admission to general hospitals, where appropriate.

X. INTERSTATE COOPERATION

1. Patients should be treated in the locale which is determined to be best for them therapeutically, rather than on the basis of residence requirements. The states, therefore, are urged to adopt the interstate Compact on Mental Health.

2. In an increasing number of locations in various parts of the country, large municipal complexes cross state lines, requiring—for greatest usefulness and economy—the operation cooperatively of comprehensive mental health centers by adjoining states. The Interstate Compact on Mental Health provides for such

cooperative arrangements and should be applied in appropriate areas. We urge Congress to enact legislation to permit federal participation in the financing of interstate facilities built pursuant to an interstate compact, on the same basis as now available to individual States.

XI. FINANCING

1. The Joint Commission on Mental Illness and Health has recommended that the local, state, and federal governments work together to triple the expenditures in the field of mental illness over the next ten years. No set figure can be uniformly applied to all of the states, but it is obvious that substantially greater sums must be appropriated by all levels of government to accomplish the objectives stated in this policy declaration.

2. The states must encourage the support of nongovernment hospitals, clinics, and various related services for the mentally ill.

XII. MENTAL HEALTH INSURANCE

We shall ask our Insurance Commissioners to request companies admitted to do business in our respective states to review their health insurance plans with a view to including coverage of mental illness.

XIII. ACTION BY THE GOVERNORS' CONFERENCE

1. We recommend that the Executive Committee of the Governors' Conference be requested to draw attention to the findings of this special Governors' Conference on Mental Health and that the next annual meeting of the Governors' Conference recommend the establishment of a Standing Committee on Mental Health.

2. We commend and express gratitude to the members of the medical profession and all other persons who serve the states and nation in public mental health facilities and programs. Their service and their cooperation with Governors and legislators have contributed substantially to the significant progress of mental health programs within the states and nation.

[Reprinted from the Modern Hospital, March 1961]

ACTION FOR MENTAL HEALTH[1]

(Digest of Final Report of Joint Commission on Mental Illness and Health)

The Mental Health Study Act of 1955 directed the Joint Commission on Mental Illness and Health, under grants administered by the National Institute of Mental Health, to analyze and evaluate the needs and resources of the mentally ill people of America and make recommendations for the national mental health program.

The purpose of this final report is to arrive at a program that would approach adequacy in meeting the needs of the mentally ill—to develop a plan of action, in other words, that would satisfy us that we are doing the best we can toward their recovery.

The latter is not at present the case. We have not been able to do our best for the mentally ill to date, nor have we been able to make it wholly clear what keeps us from doing so. Attempts to provide more humane care for the mentally ill and to transform "insane asylums" into hospitals and clinics true to the healing purpose of medicine have occurred periodically during the last two centuries. While each reform appears to have gained sufficient ground to give its supporters some sense of progress, each has been rather quickly followed by backsliding, loss of professional momentum, and public indifference.

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[1] This Digest is a 10,000-word condensation of Action for Mental Health, a 100,000-word report made to Congress, the Governors, and the Legislatures of the United States. The Digest is provided as a convenience to public officials and the press, who require a quick impression of the findings and recommendations contained in the full report. Under no other circumstance, however, does the Digest constitute an appropriate substitute for the thoughtful and extensive analysis to be found in Action for Mental Health. For documentation of statements in this Digest, the interested reader is referred to the full work, published by Basic Books Incorporated, 59 4th Avenue, New York 3, N.Y. $6.75.

Even if we can find the road to a substantial reduction in the human and economic problems of mental illness, we are obliged to remain in full view of certain intervening observations that provide little cause for hope except as we can dispose of them. We must note, for instance, the curious blindness of the public as a whole and of psychiatry itself to what in reality would be required to fulfill the well publicized demand that millions of mentally ill shall have sufficient help in overcoming the disturbances that destroy their self-respect and social usefulness.

Further, we must rise above our self-preservative functions as members of different professions, social classes, and economic philosophies and illuminate the means of working together out of mutual respect for our fellow man. We each have a responsibility that is common to all—our responsibility as citizens of a democratic nation founded out of faith in the uniqueness, integrity, and dignity of human life.

WHY HAS CARE OF THE MENTALLY ILL LAGGED?

The United States Congress, in the last ten years, has given the American public a working demonstration of a new willingness to accept leadership and responsibility in active efforts to help citizens who are threatened by mental illness. The Federal Government's chief exemplifications of this demonstration may be found in the programs of the National Institute of Mental Health and the Veterans' Administration. The good example has been followed in the efforts of state legislatures, governors, and their public health, mental health, and public welfare agencies in many states.

It is tempting to congratulate ourselves on the gains scored—in increased amounts of money spent for mental health research, in the increases in mental health personnel, in the beneficial effects of the new drugs. But the demand for public mental health services is still largely unmet, despite the gains.

One of the most revealing findings of our mental health study is that comparatively few of 277 state hospitals—probably no more than 20 percent—have participated in innovations designed to make them therapeutic, as contrasted to custodial, institutions. Our information leads us to believe that more than half of the patients in most state hospitals receive no active treatment of any kind designed to improve their mental condition. This is the core problem and unfinished business of mental health. Eight of every ten mental hospital patients are in state institutions. These hospitals carry a daily load of more than 540,000 patients, and look after nearly a million in a year's time.

Commonly, a clearly defined, well established public demand and need for a particular health program is sufficient to stimulate aggressive public action toward its support and progressive steps to organize whatever high-quality facilities may be needed. Quick responsiveness in meeting the demand is not characteristic in the mental illness field, however.

Mental illness, commonly regarded as America's No. 1 health problem, ranked fourth in the categorical interests of the National Institutes of Health in 1950, as measured by dollars spent; by 1960, it had risen to second, behind cancer (see table 1). The gains of the voluntary campaign have not been commensurate, however. Voluntary mental health funds ranked eighth at the beginning and seventh at the end of the period, and were eighth in grand total, as shown in table 2.

Over a ten-year period, poliomyelitis had the greatest public appeal, followed by tuberculosis, cancer, heart disease, crippled children, cerebral palsy, muscular dystrophy, and mental health, in that order.

Despite the repeated snakepit exposés and the great amount of attention given to mental illness by the press, surveys have shown that mental illness has had a lower reader impact than has heart disease, cancer, or polio.

Despite the "big push" in recent years to do something about major mental illness, the average proportion of general state expenditures and of state health expenditures going for the care of mental hospital patients actually declined.

TABLE 1.—*Total appropriations of Congress for major activities of the National Institutes of Health, 1950–61* [1]

[In millions of dollars]

Fiscal year	Cancer	Mental	Heart	General	Arthritis [2]	Allergy [2]	Neurology [2]
1950	18.9	8.7	10.7	12.0			
1951	20.0	9.5	14.2	14.3			
1952	19.6	10.5	10.0	15.7			
1953	17.9	10.9	12.0	16.6			
1954	20.2	12.1	15.2	4.7	7.0	5.7	4.5
1955	21.7	14.1	16.7	4.7	8.2	6.1	7.6
1956	25.0	18.0	18.9	5.9	10.8	7.8	9.9
1957	48.4	35.1	33.4	12.1	15.9	13.2	18.7
1958	56.4	39.2	35.9	14.0	20.3	17.4	21.3
1959	75.3	52.4	45.6	29.0	31.2	24.0	29.4
1960	91.2	68.1	62.2	46.0	46.9	34.0	41.4
1961	111.0	100.9	86.9	83.9	61.2	44.0	56.6
Total	525.6	379.5	361.7	258.9	201.5	152.2	189.4

[1] Source: DHEW-PHS-National Institutes of Health operating appropriations by activity, 1950 through 1961. From Office of the Director, NIMH.

[2] Arthritis, allergy and infectious diseases, neurology and blindness became separate categories in 1954.

TABLE 2.—*Total funds raised nationally in 10 leading voluntary health campaigns 1950–59* [1]

[In millions of dollars]

	Polio	Tuberculosis	Cancer	Heart	Crippled children	Cerebral palsy	Muscular dystrophy	Mental health [2]	Arthritis	Multiple sclerosis
1950	30.8	21.0	13.9	4.1	5.8	1.0	(3)	(4)	0.7	0.18
1951	33.5	21.7	14.6	5.5	6.1	2.1	(3)	0.7	1.0	.19
1952	41.4	23.2	16.4	6.7	6.7	4.0	0.26	.6	1.0	.25
1953	51.4	23.8	19.8	8.5	7.7	6.4	.6	[5] .7	1.4	.45
1954	65.0	24.0	21.7	11.3	8.1	8.2	4.0	[5] 1.7	1.5	.8
1955	52.5	24.6	24.4	13.6	8.5	7.5	3.9	2.4	1.8	1.3
1956	51.9	25.8	27.2	17.5	9.8	8.1	3.0	2.6	2.2	2.0
1957	44.0	26.3	29.6	20.5	10.3	8.4	3.7	3.8	2.4	2.3
1958	35.4	26.0	29.7	22.3	10.4	9.2	4.9	4.5	3.0	2.5
1959	[6] 31.3	26.0	[6] 31.0	24.0	10.3	9.5	4.6	[6] 5.5	3.6	(7)
Total	437.2	242.4	228.3	134.0	83.7	64.4	24.96	22.5	18.6	9.97

[1] "Rough" figures supplied by National Information Bureau for (1) National Foundation, (2) National Tuberculosis Association, (3) American Cancer Society, (4) American Heart Association, (5) National Association for Crippled Children and Adults, (6) United Cerebral Palsy Association, (7) Muscular Dystrophy Association of America, (8) National Association for Mental Health, (9) Arthritis and Rheumatism (10) National Multiple Sclerosis Society.

[2] Figures for 1951 and 1952 from National Information Bureau, for 1953–59 from National Association for Mental Health.

[3] No campaign.

[4] Not available due to merger.

[5] Approximate.

[6] Estimate.

[7] Not available.

TABLE 3.—*Movement of patient population in public mental hospitals, United States, 1956–59*

Item	1956	1957	1958	1959	Percent change		
					1956–57	1957–58	1958–59
All admissions	185,597	194,497	209,503	223,225	4.8	7.7	6.5
First admissions	125,539	129,278	137,061	142,881	3.0	6.0	4.2
Readmissions	60,058	65,219	72,442	80,344	8.6	11.1	10.9
Discharges	133,208	145,116	161,972	175,727	8.9	11.6	8.4
Deaths in hospital	48,236	46,848	51,294	49,640	−2.9	9.5	−3.2
Resident patients at end of year	551,390	548,626	544,863	542,721	−.5	−.7	−.4
Personnel employed full time at end of year	153,715	162,753	169,438	174,218	5.9	4.1	2.8
Maintenance expenditures:							
Total	$663,280,934	$731,875,462	$805,861,786	$854,354,503	10.3	10.1	6.0
Per patient	$1,194.88	$1,332.31	$1,475.26	$1,577.54	11.5	10.7	6.9

The quality of care given these patients may be judged from the fact that State hospitals spend an average of $4.44 per patient per day compared to $31.16 for community general hospitals and $12 or more per patient-day both for tuberculosis and Veterans' Administration psychiatric hospitals. Likewise, State hospitals have the lowest ratio of hospital personnel to patients, 0.32 per patient as compared to 2.1 in community general hospitals.

For the last 4 years, there has been a net decrease in the number of patients living in State hospitals. (See Table 3.) This trend primarily reflected the benefits of tranquilizing drugs, the drugs making it possible to increase the number of patients who can be released from the hospital. However, since the number of patients admitted to these hospitals has continued to climb, the net decrease in the hospitals' population cannot be said to represent a reduction in the mental illness problem. What has occurred is an increase in the turnover and a shift in the whereabouts of mental patients. More are being maintained at home or treated elsewhere.

There are two ways to measure progress: from the standpoint of how far we have come, or from the standpoint of how far we yet have to go. By the first measure, we have made progress. By the second measure, we have little cause for self-congratulation and no cause for relaxation of efforts.

The first and pivotal question in appraising where we now stand and next should go is this: Why have our efforts to provide effective treatment for the mentally ill lagged behind our objectives, behind public demand, and behind attacks on other major health problems?

WITH PROPER TREATMENT, THE SCHIZOPHRENIC PATIENT HAS THREE-IN-FIVE CHANCE OF LEADING A USEFUL LIFE IN THE COMMUNITY

We began with the statement that we have not done as well as we know how for the major mentally ill, in terms of humane and healing care. This is to say that if all, or most, had the benefit of modern treatment, more patients would recover or show improvement. Palpably, if this assumption is untrue then we have no immediate incentive for greater efforts to reduce lag and accelerate progress.

Actually, the typical patient with schizophrenia or other functional psychosis (so called because no organic cause is known) has a much better outlook than do patients with some of the better known chronic degenerative diseases, such as cancer of the lung or stomach.

Treatment of mental illness stands on two rational pedestals, one social and one medical—humanitarianism and science.

Modern methods of treatment of major mental illness seek to systematize and capitalize on a historic trend away from punishment and toward "moral treatment," based on humane consideration for the patient as an individual and member of society. No longer does progressive psychiatry hold with the early dictum that "terror acts powerfully on the body through the medium of the mind, and should be employed in the cure of madness." We do still see residual manifestations of this latter approach in shock treatments.

To moral treatment has been added both psychotherapeutic and sociological insight into how patients may be treated, either individually or in groups, to bring about solutions of their problems of living with themselves and with others. To psychotherapy and social therapy (the "therapeutic community") have been added the tranquilizing drugs, which may be described as "moral treatment in pill form." These drugs quiet the patient and make him more agreeable and easier to work with. In summary of what we know about the treatment of the major mental illnesses which fill our public mental hospitals, we may say:

1. The persistent attitude that schizophrenia is a hopeless, incurable disease requiring the patient to be removed from human society for the rest of his life is baseless.
2. The idea that the patient is totally insane is likewise without foundation. Medical psychology has consistently observed and generally accepts the fact that functional psychosis involves only certain of the components of the personality. The patient is sick in some ways and healthy in others. Rational treatment directs itself toward salvaging the healthy and reducing the sick parts of the mind.
3. Human beings regard loss of liberty, forcible detention, removal from the community, and imprisonment as punishment for wrongdoing; the mentally ill are no exception. It is generally agreed that the typical locked-ward State hospital, centering its interest on the physical rather than the mental welfare of the patient, increases the patient's disability by reinforcing rather than counteracting public pressure to reject the patient from the community. As a pioneer reformer, Clifford Beers, said, "Madmen are too often man made." The open hospital, with unlocked wards, is one antidote to this disabling process. Another is treatment in mental health clinics of patients not actually requiring hospitalization. Many of the patients in State hospitals do not need to be there.
4. The insistent professional preoccupation with "cures" presents a blind alley. The present state of our scientific knowledge does not permit psychiatry as yet to formulate exact tests of cure. The outlook for the schizophrenic, the main source of the long-term accumulation of patients in State hospitals, is not poor but good under optimum treatment conditions. He has a one-in-five chance of spontaneous recovery without systematic treatment. Through proper treatment, he has at least a three-in-five and perhaps as much as four-in-five chance of improving sufficiently to lead a useful life in his community.

MANY PEOPLE—INCLUDING PHYSICIANS—FIND IT HARD TO RECOGNIZE PSYCHOLOGICAL ILLNESS AS ILLNESS

The way society handles its mentally ill has been the subject of scandalized attack many times. But, as already implied, repeated exposure of the shameful, dehumanized condition of the mentally sick people who populate the back wards of State hospitals does not arouse the public to seek sweeping humanitarian reforms, let alone stimulate widespread application of modern methods of treatment. Presumably, if we can answer why there has not been a strong public response (as there has been, for example, in the campaigns against tuberculosis, cancer, and heart disease) we then can determine why effective treatment for the mentally ill has lagged.

The answer, according to our analysis in the following pages, is that the mentally ill are singularly lacking in appeal. They tend to disturb or offend other people and, when they do, people generally treat them as disturbers and offenders and, of course, as if they were responsible for their behavior. In contrast, it has been the special view of the mental health professions that people should understand and accept the mentally ill and do something about their plight.

The public has not been greatly moved by this protest. People do feel sorry for the mentally ill, but, in the balance, they do not feel as sorry as they do relieved to have out of the way persons whose behavior disturbs and offends them. Patients with major mental illness come to be viewed as "impossible people" and mental institutions as places where they are sent when their families and communities "no longer can stand them."

The fact that society tends to reject the mentally ill is, of course, well known; little significance seems to have been attached to it, however. The full reach of the rejection mechanism is little recognized and even denied by some who have learned to overcome it in their own professional relations with persons suffering mental disturbances or disorders.

We can name a number of processes, all of which add up to, or reinforce, the fact that the mentally ill repel more than they appeal. One characteristic of a psychotic is that he becomes a stranger among his own people. Since antiquity mankind has been prone to feel hostility toward the stranger, and this applies equally to any persons who behave strangely. A social system depends on order, and order depends on predictability in the behavior of one's fellows.

Normal persons for the most part want to do what they have to do to "get along." The typical psychotic does not. In consequence, society conventionally closes ranks against him. Identified major mental illness carries a stigma that cuts the bonds of human fellowship.

Many other diseases—tuberculosis, syphilis, cancer, for example—have at times stigmatized their victims. But the stigma of a disease recognized to be physical and lethal tends to disappear, or be offset, as it becomes better understood and publicly attacked. The reason, as we analyze it, is not that science has found causes and cures—the causes and cures of cancer and the leading forms of heart disease are still the subject of an intensive search.

Rather, the physically sick person fits society's deep-seated conception of a sick person. Feeling helpless, he turns to others for help and, receiving help, is responsive to it. He evokes sympathy. Commonly, the acutely ill psychotic does not appear to want help or accept help but, quite the reverse, thinks he is not sick and may interpret "help" as "harm." He repels sympathy. He is mad.

This lack of appeal has many dimensions. The rise of state hospitals and their persistence, despite all efforts to reform them, is the most outstanding example. Mental health authorities are in general agreement that society uses these huge institutions as dumping grounds for social rejects, rather than as true hospitals.

A rejection effect may also be detected in the rise of the mental hygiene movement. Its founder, Clifford Beers, as his book "A Mind That Found Itself" clearly reveals, intended the movement to be primarily one of stopping brutal treatment of the mentally ill and converting mental hospitals into humane, healing institutions. It did not become so. Attention became focused on mentally healthy living rather than help for the sick.

The mentally ill's lack of appeal as a public cause has been reflected in a lack of strong leadership and strong organization in the voluntary mental health movement, some state organizations excepted. An organization can hardly develop and mature, as a matter of fact, if followers or members cannot be persuaded in sufficient numbers to identify with the cause at hand. It has been observed that the mentally ill are inherently handicapped in any effort to form a strong public pressure group. Lacking in a reasonable capacity to get along with other people. they find organization behind a leader to be difficult, if not impossible. The friends or relatives are equally immobilized through an aversion to identifying themselves with the mentally ill.

Several studies of public attitudes have shown a major lack of recognition of mental illness as illness, and a predominant tendency toward rejection of both the mental patient and those who treat him. There is a general agreement on these points in contrast to the lack of confirmation often characterizing parallel studies in the mental health field. (It is encouraging to note, however, that these negative attitudes are less among younger and better educated persons than the older and less educated groups.)

The circle of negligence and indifference becomes complete when we recognize that many members of learned professions are likewise prone to turn their back on the core problem of major mental illness.

General practictioners as well as other members of the medical profession have been found in a majority of instances to be both uninformed and unsympathetic when they are confronted with mental illness. The same observation applies, oddly enough, to many psychiatrists in private practice when we narrow discussion to the core problem of severe mental illness. The main concern of the popular psychonalyst is with neurosis rather than psychosis; this is also true of other types of psychiatrists in private practice. Their major focus is on minor and more easily treatable forms of mental illness. Even mental hospital superintendents themselves, it has been noted, may share the public's stigmatizing attitudes toward mental patients.

In summary, we need to become conscious, at the action level, of two points if we are to overcome the lag in the care of the mentally ill: (1) People find it difficult to think about and recognize psychological illness as illness or to see sickness as having psychological forms. (2) The major mentally ill as a class lack in appeal, which is to say that they are overburdened with liabilities as persons and as patients.

To explain the first point: Man is prima facie an outward-looking, tool-operating, thing-oriented creature, the man of science not excepted. We use our unique human intelligence principally to think about picturable, tangible, concrete, measurable, recordable things. Recent anthropological and neurological evidence indicates that tools were used by prehistoric apes in the absence of a human brain, and that continued use of tools may have conditioned the way in which the human brain evolved. Also, the interpretation is borne out by the more rapid advancement of the physical and mathematical than of the behavioral and social sciences, and by the fact that the most crucial questions facing mankind today involve psychological and social conduct. In any event, education of the average man appears to favor greater understanding of matter than of mind. Most of us are in this way psychologically handicapped persons, mentally blind to our physical bias.

To elaborate the second point: It is not so much his symptoms themselves that bring the psychotic patient into a mental hospital—many people in the general population have equally strange symptoms—but that his behavior reaches a point where people no longer can stand it. Violence is more the exception than the rule, popular misconceptions to the contrary. It is basically that normal people are disturbed by the patient's refusing to comply with expectations of time and place. Challenged by the problem, the psychiatrist in the hospital nonetheless may find the patient uncooperative—too wearing, too trying, too tiring. Thus the most conscientious and devoted doctor may be forced to turn his back on the patient, completing the circle of rejection.

It should now be clear that one way around the impasse of public and professional attitudes that we appear to have erected would be to emphasize that persons with major mental illness are in certain ways *different* from the ordinary sick. With such an understanding and agreement, it might then be possible to proceed in the light of fuller reason to adopt more helpful attitudes.

THE MENTALLY ILL USUALLY BEHAVE IRRESPONSIBLY; SOCIETY USUALLY BEHAVES TOWARD THEM THE SAME WAY

It is commonly stated that one in ten is mentally ill or psychologically disturbed. When this estimate is limited to those with severe disorders that are socially disruptive or individually incapacitating, the ratio is perhaps one in 100. Society has organized itself and its handling of the one in 100 out of primary concern for the 99 who do not disturb their fellow men sufficiently to acquire the mental patient label. This does not mean, however, that we would long hesitate in modifying the system of exiling and thereafter dehumanizing patients whose illness makes them socially unacceptable if we could be shown that a more desirable alternative is available.

The current trend, among more progressive mental health professionals and interested laymen, is to recognize and to pursue alternatives—to demonstrate that negative public attitudes are not insurmountable roadblocks; to show that it is possible to develop and practice friendly and accepting attitudes toward the mentally ill; to show that it is possible to work with them, to treat them as human beings, and get good results. For example, during the last six years more than 1,000 volunteer students from Harvard and Radcliffe colleges and Brandeis University have worked regularly with chronic psychotics at Metropolitan State Hospital in Waltham, Mass. They have been active in ward improvement projects and as case aides—without harm to themselves or the patients. On the contrary, there has been a mutual benefit, in the notable improvement of patients and higher motivation of students, some of whom have chosen mental health as their career work. Many other examples of lay volunteers who work with mental patients could be cited.

It is a characteristic of the mentally ill that they behave in an irresponsible manner; it is a characteristic of society that we behave toward them in the same manner. The findings of the various projects undertaken as part of the Joint Commission's mental health study bear out our belief that this circle of rejection can be broken. Indeed, there are many signs that the process is well under way.

In all categories of service—hospitals, clinics, community agencies, schools, for example—we found a tremendous demand for authoritative information about mental illnesses and for excess to available services. Waiting lists are the rule. It is a demand that we have not begun to meet. Only in the meeting of it will we have the opportunity of large-scale demonstration that public attitudes can be improved and mentally troubled persons can be helped.

In our nationwide survey of the American people's views of their own mental health, one in four adults disclosed he at some time had had a psychological problem in which professional help would have been useful. One out of seven actually sought help—mainly for problems involving marriage, personal adjustment, or children. Forty-two percent of those who sought help turned to their clergymen, 29 percent to physicians in general, 18 percent to psychiatrists and psychologists, and 10 percent to social agencies and marriage clinics.

More than half of these troubled persons were sure that they had been helped—more in problems they saw as physical or external to them than as psychological or within themselves. But more were helped in making personal adjustments than in solving marital troubles.

The foregoing study together with our studies of community services, churches and schools indicated the following: While the younger generation and better educated persons have greater recognition of the psychological nature of many of their problems and therefore see the need to deal with them psychologically, the demand for such services is not being met. Indeed, mental health facilities and skills are inadequate wherever one looks, whether to mental or general hospitals, clinics, counseling services, clergymen, family doctors, special rehabilitation services, or elsewhere.

Much information has been disseminated. Many meetings have been held. But the shortage of trained mental health personnel works totally against the purposes of mental health education. Increased mental health education only serves to tax already inadequate mental health services.

The Joint Commission made an intensive study of the demand for and supply of mental health professional manpower—particularly psychiatrists, psychologists. psychiatric nurses, and psychiatric social workers. This study made forcibly clear that the great shortages of manpower in these categories is inextricably related to the shortage of professional manpower in general—teachers, lawyers, physicians, scientists, technologists. And the professional manpower shortage is related to defects in our system of public school and college education. Most importantly, a large part of the nation's potential brainpower is being lost between high school and college. In fact, only about one-tenth of American youth become college graduates; only one-third of those of outstanding intelligence in high school go on to finish college.

It is of special interest to a national mental health study, we may say in passing, that our culture does not manifest a great respect for the mind. Our minds, the findings indicate, seem to be of small moment to us, whether normal or sick. The critical problem is one of intellectual motivation. What examples do we set? What new challenge do we offer? What spiritual rewards do we offer? What degree of economic security do we provide?

Our manpower study concluded, with frank pessimism, that sufficient professional personnel to eliminate the glaring deficiencies in our care of mental patients will never become available if the present population trend continues without a commensurate increase in the recruitment and training of mental health manpower. The only possibilities for changing this negative outlook for hundreds of thousands of mental hospital patients would require a great change in our social attitudes, and a consequent massive national effort in all areas of education, including large increases in the number of persons engaged in mental health work, or a sharp breakthrough in mental health research.

A Sound Research Attack on Mental Illness Must Be Mounted on a Long-Term Base

The demand for professional services for the custody and continuous care of patients with schizophrenia or cerebral arteriosclerosis could be greatly reduced by a major breakthrough in the prevention or treatment of either of these conditions with a biochemical or other technic that could be administered to large numbers by a single therapist. Together, these patients fill the great majority of mental hospital beds.

But even with maximum research support, we cannot count on increased purchasing power in the science market to produce the desired result within a given time. A characteristic of scientific research is that it ultimately produces results of potential benefit to us all, but we cannot predict when the result will come or even that it will be the one we are looking for. There was a lag of 40 years between the time Karl Landsteiner discovered the cause of poliomyelitis and when John Enders' group accomplished the tissue-culture breakthrough that made production of a polio vaccine possible. Sir Alexander Fleming was not looking for a penicillin when be observed its effects, and yet the antibiotics have made more difference in the control of infectious diseases than any other drug in medical history. It was research in anesthesia and motion sickness rather than mental health that brought us the tranquilizing drugs.

Our purpose here is not to be defeatist; only realistic. The enormous task of taking care of mental patients is matched by the enormous research lag in the study of human behavior. Only by making the research possible can we hope to overcome the lag. What we mean is that our total national investment in mental health research—in time, money, men, and research and training facilities—simply does not measure up to the need for useful and reliable knowledge that could form the foundation of future progress.

The mental health sciences address themselves to the alleviation of a complex of biological, psychological, and sociological problems that have plagued man through his history; mental health scientists face this task with an incredibly small fund of knowledge about causes and cures. It is a field where much-qualified guesses abound and general agreement is difficult to obtain.

A sound research attack on problems of mental illness and mental health can be mounted on no other base than a long-term one. The prospect of a crash program and a quick breakthrough is not realistic in the absence of a vast increase in basic knowledge. We have the examples in other fields, such as cancer and heart disease, where intensified research has been going on for some years in response to an earlier public focus of effort to solve these health problems. Hopes have been high and have remained so. Yet even in these areas the quick fulfillment of grand objectives is not yet at hand.

We can again illustrate our point via the major advance represented by introduction of the tranquilizing drugs, now used in the treatment of probably one-third of all mental hospital patients. Although these drugs quiet the patients, inspire hopefulness, and make mental hospital employment more interesting and attractive, they do not relieve but rather increase the need for professional experience and skills. The effects of the drugs must be closely watched and evaluated, for they are not without harm. At the same time, they make many more patients accessible to psychotherapy, rehabilitation, and discharge from the hospital. Such drugs actually increase the need for trained therapists and helping personnel.

In making a statement of the aims and strategy for a more effective research effort in the mental health field, certain characteristics of the research enterprise must be taken into account.

One characteristic is the great diversity of persons, sciences, methods, and goals involved in "mental health research."

Another characteristic is the sharp cleavage in attitudes about *basic* and applied research: Basic research is defined as any scientific inquiry for the purpose of discovering and generalizing truths about the essence of nature, including man; applied research here refers to studies directed primarily toward the practical problems of preventing mental illness or treating mental patients. This cleavage leads to a neglect of basic research as impractical or unpromising, and to the false assumption that basic research should be done in universities; applied research, in hospitals.

Efforts should be made to increase communication between researchers and practitioners. Their differing interests and training at present lead them in opposing directions. One result is poorly designed or "sloppy" clinical research. Actually, research is a service to practitioners as well as to the patients served.

Our study shows that the mental health research output is concentrated in a relatively small number of major universities and their medical centers. Smaller colleges and state mental hospitals account for an extremely small portion of the total research effort. There should be support for *flexible* and *experimental* programs of *stimulating* research in many different areas and settings.

The mental health sciences are preponderantly dependent on the federal government for their financial support, and becoming more so. The greatest single source is the National Institute of Mental Health. The federal percentage of total support for mental health research in 1958 was 57 percent; the state percentage was 20 percent. The pharmaceutical foundations supplied 17 percent; private foundations and other sources, less than 6 percent. In 1959 and again in 1960, Congress sharply increased its NIMH appropriations.

The above figures adequately demonstrate that federal government policies determine the shape, size, direction, and soundness of the overall effort in mental health research. Current policy, emphasizing annual grants for specific projects by individual investigators, favors short-term research and applied research, as opposed to the long-term, more fundamental approach needed.

The present effectiveness of our mental health services is seriously limited by large gaps in our scientific knowledge about the fundamentals of mental illness and mental health. Our research recommendations therefore will concern themselves with the particular kinds of support needed to fill the gaps as fast as possible.

SCIENCE AND EDUCATION ARE RESOURCES THAT MUST HAVE ADEQUATE SUPPORT FROM HUMAN SOCIETY, WHETHER PUBLIC OR PRIVATE

The philosophy the federal government needs to develop and crystallize is that science and education are resources—like natural resources. They can meet an ends test but not a means test or a time schedule. Science and education operate not for profit but profit everybody; hence, they must have adequate support from human society, whether public or private. The following recommendations are designed to help achieve this:

RECOMMENDATIONS

1. A much larger proportion of total funds for mental health research should be invested in basic research as contrasted with applied research. Only through a large investment in basic research can we hope ultimately to specify the causes and characteristics sufficiently so that we can predict and therefore prevent or cure various forms of mental illness or disordered behavior.
2. Congress and the state legislatures should increasingly favor long-term research in mental health and mental illness as contrasted with short-term projects.
3. Increased emphasis should be placed on, and greater allocations of money be made for, venture, or risk, capital both in the support of persons and of ideas in the mental health research area.
4. The National Institute of Mental Health should make new efforts to invest in, provide for, and hold the young scientist in his career choice. This recommendation would require that more full-time positions be supported for ten-year periods as well as some on the basis of lifetime appointments.
5. Support of program research in established scientific and educational institutions, as initiated by the National Institutes of Health, should be continued and considerably expanded in the field of mental health.
6. The federal government should support the establishment of mental health research centers, or research institutes operated in collaboration with educational institutions and training centers, or independently.
7. Some reasonable portion of total mental health research support should be designated as capital investment in building up facilities for research in states or regions where scientific institutions are lacking or less well developed.
8. Diversification should be recognized as the guiding principle in the distribution of federal research project, program, or institute grants from the standpoint of categories of interest, subject matter of research, and branches of science involved.

THE LAG IN TREATING THE MENTALLY ILL IS REFLECTED IN THE CONTINUED EXISTENCE OF CUSTODIAL CARE HOSPITALS

The patient care portion of our study centers on new patterns in the treatment of the mentally ill in the community and in institutions. These patterns, which together comprise the current trend in care of the mentally ill, involve:

Providing immediate help for the emotionally disturbed.

Extending the care of mental patients into the community via clinics and other agencies.

A broader conception of what constitutes treatment.

Individualizing of patient care in mental hospitals.

The breaking down of barriers between the hospital and the community—in effect, the open-hospital movement.

The development of a therapeutic milieu in mental hospitals—social treatment.

Development of aftercare programs concerned with adequately supporting the patient so he can remain in the community or return there.

The practitioners who are developing new treatment programs believe in them and hope that they will result in better care and more effective treatment. The one constant in each new method appears to be the enthusiasm of its proponents, and most probably such enthusiasm transmits itself to patients in beneficial ways.

The salient characteristic of the best available treatment of psychotics, as we now understand it, is that some kind of relationship—psychological or social—takes place between the patient and the helping person. This relationship can be formed by informed laymen working individually or in groups under the guidance of psychiatrists, clinical psychologists, or psychiatric social workers, as well as by these and other classes of mental health workers—for example, nures, attendants, and occupational and recreational therapists.

But programs reflecting newer concepts of treatment are relatively rare and unevenly distributed, with the large majority of State hospitals remaining custodial and punitive in their approach. The thesis of ACTION FOR MENTAL HEALTH, that the lag in the treatment of the mentally ill reflects a fundamental pattern of social rejection, is nowhere better evidenced than by the continued existence of these "hospitals" that seem to have no defenders but endure despite all attacks.

To achieve better care of patients, the mental hospital needs to be integrated into the community. This means keeping the hospital and its staff in closer touch with all the community's public and private service agencies. It means an end to the hospital's isolation from the community; in isolation, the backward, custodial system may thrive, whereas the mainstream of community activity, a hospital's shortcomings may come to attention.

The State hospital must cease to be treated as a target for political exploitation. Patronage must end. These hospitals and their logical community extensions—clinics and after-care programs—must be manned in all cases by properly motivated career workers and not by hacks, professional, or lay. These workers need to be well trained and well paid; they need the opportunity to do a good job and hence to demonstrate to the public what they can do.

The newer programs do nothing to solve the manpower problem, although they indicate the direction in which a solution may lie. This brings us to recommendations for improved care of the mentally ill.

A National Mental Health Program Should Avoid the Risk of False Promise in Public Education

RECOMMENDATIONS

1. Policy

In the absence of more specific and definitive scientific evidence of the causes of mental illnesses, psychiatry and the allied mental health professions should adopt and practice a broad, liberal philosophy of what constitutes and who can do treatment within the framework of their hospitals, clinics, and other professional service agencies, particularly in relation to persons with psychoses or severe personality or character disorders that incapacitate them for work, family life, and everyday activity. All mental health professions should recognize:

A. That certain kinds of medical, psychiatric and neurological examinations and treatments must be carried out by or under the immediate direction of psychiatrists, neurologists, or other physicians specially trained for these procedures.

B. That psychoanalysis and allied forms of deeply searching and probing "depth psychotherapy" must be practiced only by those with special training, experience and competence in handling these technics without harm to the patient (namely, by physicians trained in psychoanalysis or intensive psychotherapy plus those psychologists or other professional persons who lack a medical education but have an aptitude for, adequate training in, and demonstrable competence in such technics of psychotherapy).

C. That nonmedical mental health workers with aptitude, sound training, practical experience, and demonstrable competence should be permitted to do general, short-term psychotherapy—namely, the treating of persons by objective, permissive, nondirective technics of listening to their troubles and helping them resolve these troubles in an individually insightful and socially useful way.

Such therapy, combining some elements of psychiatric treatment, of client counseling, of "someone to tell one's troubles to," and of love for one's fellow man, obviously can be carried out in a variety of settings by institutions, groups and by individuals, but in all cases should be pursued under the auspices of recognized mental health agencies.

2. Recruitment and training

The mental health professions need to launch a national manpower recruitment and training program, expanding on and extending present efforts and seeking to stimulate the interest of American youth in mental health work as a career. This program should include all categories of mental health personnel. This program should emphasize not only professional training but also short courses and on-the-job training in the subprofessions and upgrading for partially trained persons.

3. Services to mentally troubled people

Persons who are emotionally disturbed—that is to say, under psychological stress that they cannot tolerate—should have skilled attention and helpful counseling available to them in their community if the development of more serious mental breakdowns is to be prevented. This is known as secondary prevention, and is concerned with the detection of beginning signs and symptoms of mental illness and their relief; in other words, the earliest possible treatment. In the absence of fully trained psychiatrists, clinical psychologists, psychiatric social workers, and psychiatric nurses, such counseling should be done by persons with some psychological orientation and mental health training and access to expert consultation as needed.

4. Immediate care of acutely disturbed mental patients

Immediate professional attention should be provided in the community for persons at the onset of acutely disturbed, socially disruptive, and sometimes personally catastrophic behavior; that is, for persons suffering a major breakdown. The few pilot programs for immediate, or emergency, psychiatric care now in existence should be expanded and extended as rapidly as personnel becomes available.

5. Intensive treatment of acutely ill mental patients

A national mental health program should recognize that major mental illness is the core problem and unfinished business of the mental health movement, and that among those with severe mental illnesses the intensive treatment of those with critical and prolonged breakdowns should have first call on fully trained members of the mental health professions. There is a need for expanding treatment of the acutely ill mental patient in all directions, via community mental health clinics, general hospitals, and mental hospitals, as rapidly as psychiatrists, clinical psychologists, psychiatric nurses, psychiatric social workers, and occupational, physical and other nonmedical therapists become available in the community.

A. Community Mental Health Clinics.—Community mental health clinics serving both children and adults, operated as outpatient departments of general or mental hospitals, as part of state or regional systems for mental patient care, or as independent agencies, are a main line of defense in reducing the need of many persons with major mental illness for prolonged or repeated hospitalization. Therefore, a national mental health program should set as an objective one fully staffed full-time mental health clinic available to each 50,000 of population. Greater efforts should be made to induce more psychiatrists in private practice to devote a substantial part of their working hours to community clinic services, both as consultants and as therapists.

B. General Hospital Psychiatric Units.—No community general hospital should be regarded as rendering a complete service unless it accepts mental patients for short-term hospitalization and therefore provides a psychiatric unit or psychiatric beds. Every community general hospital of 100 or more beds should make this provision. A hospital with such facilities should be regarded as an integral part of a total system of mental patient services in its region.

It is the consensus of the Mental Health Study that definitive care for patients with major mental illness should be given if possible, or for as long as possible, in a psychiatric unit of a general hospital and then, on a longer term basis, in a specialized mental hospital organized as an intensive psychiatric treatment center.

C. Intensive Psychiatric Treatment Centers.—Smaller state hospitals, of 1,000 beds or less and suitably located for regional service, should be converted as rapidly as possible into intensive treatment centers for patients with major mental illness in the acute stages or with a good prospect for improvement or recovery if the illness is more prolonged. All new state hospital construction should be devoted to these smaller intensive treatment centers.

6. Care of chronic mental patients

No further state hospitals of more than 1,000 beds should be built, and not one patient should be added to any existing mental hospital already housing 1,000 or more patients. It is recommended that all existing state hospitals of more than 1,000 beds be gradually and progressively converted into centers for the long-term, combined care of persons with chronic diseases, including mental illness. This conversion should be completed in the next ten years.

Special technics are available for the care of the chronically ill and these technics of socialization, relearning, group living, and gradual rehabilitation or social improvement should be expanded and extended to more people, including the aged who are sick and in need of care, through conversion of state mental hospitals into combined chronic disease centers.

It would be necessary to provide the intensive treatment services for the acutely ill, outlined in the preceding section, before large state hospitals could be converted to chronic diseases. It also would be necessary to make certain changes in federal and state laws.

7. Aftercare, intermediate care, and rehabilitation services

The objective of modern treatment of persons with major mental illness is to enable the patient to maintain himself in the community in a normal manner. To do so, it is necessary (1) to save the patient from the debilitating effects of institutionalization as much as possible, (2) if the patient requires hospitalization, to return him to home and community life as soon as possible, and (3) thereafter maintain him in the community as long as possible. Therefore, aftercare and rehabilitation are essential parts of all service to mental patients, and the various methods of achieving rehabilitation should be integrated in all forms of services, among them: day hospitals, night hospitals, aftercare clinics, public health nursing services, foster family care, convalescent nursing homes, rehabilitation centers, work services, and ex-patient groups. We recommend that demonstration programs for day and night hospitals and the more flexible use of mental hospital facilities, both in the treatment of the acute and the chronic patient, be encouraged and augmented through institutional, program, and project grants.

Public information on mental illness

A national mental health program should avoid the risk of false promise in "public education for better mental health" and focus on the more modest goal of disseminating such information about mental illness as the public needs and wants in order to recognize psychological forms of sickness and to arrive at an informed opinion in its responsibility toward the mentally ill.

It is possible to make certain general recommendations about dissemination of information concerning mental illness aimed at (1) greater public understanding of the mentally ill person and those who care for him, (2) the avoiding of misunderstanding in the relations of one professional group with another, and (3) the importance of making sure, in the relations of the mental health professions with the lay public, that others understand what we are driving at.

An important point has been missed in overinsistence that the public recognize that mentally ill persons are sick, the same as if they were physically sick, and should be treated no differently from other sick persons. Mental illness is different from physical illness in the one fundamental aspect that it tends to disturb and repel others rather than evoke their sympathy and desire to help.

A sharper focus in a national program against mental illness might be achieved if the information publicly disseminated capitalized on the aspect in which mental differs from physical illness. Such information should have at least four general objectives:

1. To overcome the general difficulty in thinking and recognizing mental illness as such—that is, a disorder with psychological as well as physiological, emotional as well as organic, social as well as individual causes and effects.
2. To overcome society's many-sided pattern of rejecting the mentally ill, by making it clear that the major mentally ill are singularly lacking in appeal, why this is so, and the need consciously to solve the rejection problem.

3. To make clear what mental illness is like as it occurs in its various forms and is seen in daily life and what the average person's reactions to it are like, as well as to illucidate means of coping with it in casual or in close contact. As an example, the popular stereotype of the raving maniac or "berserk madman" as the only kind of person who goes to mental hospitals needs to be dispelled. We have not made it clear to date that such persons (who are wild and out of control) exist, but in a somewhat similar proportion as airplanes that crash in relation to airplanes that land safely.

4. To overcome the pervasive defeatism that stands in the way of effective treatment. While no attempt should be made to gloss over gaps in knowledge of diagnosis and treatment, the fallacies of "total insanity," "hopelessness" and "incurability" should be attacked, and the prospects of recovery or improvement through modern concepts of treatment and rehabilitation emphasized. One aspect of the problem is that hospitalization taking the form of ostracization, incarceration or punishment increases rather than decreases disability.

Attention is also needed to the manner in which professional persons and groups approach the public, since winning friends and support for care of the mentally ill depends first and foremost on not giving cause for offense. We recommend that the American Psychiatric Association make special efforts to explore, understand and transmit to its members an accurate perception of the public's image of the psychiatrist. Such efforts could pay a great dividend in "education of the public" if the profession were to be educated, perhaps as a part of its formal training, against overvaluing, overreaching, and overselling itself.

The primary responsibility for preparation of mental health information for dissemination to laymen should rest with "laymen" who are experts in public education and mass communications and who will work in consultation with mental health experts. But the mental health expert and the educator or mass communications expert have the primary problem of fully communicating with one another before communicating with the public. Too often the basis for discussions among mental health professionals and laymen is the easy assumption on both sides that the other fellow doesn't "understand the problem" or "know what he is talking about."

As a matter of policy, the mental health professions can now assume that the public knows the magnitude if not the nature of the mental illness problem and psychiatry's primary responsibility for care of mental patients. Henceforth the psychiatrist and his teammates should seek ways of sharing this responsibility with others and correcting deficiencies and inadequacies without feeling the need to be overbearing, defensive, seclusive or evasive. A first principle of honest public relations bears repeating: To win public confidence, first confide in the public.

HOW CAN WE MAKE STATE HOSPITALS IN FACT WHAT THEY NOW ARE IN NAME ONLY—HOSPITALS FOR MENTAL PATIENTS?

Federal, state and local expenditures for public mental patient services should be doubled in the next five years—and tripled in the next ten.

Only by this magnitude of expenditure can typical state hospitals be made in fact what they are now in name only—hospitals for mental patients. Only by this magnitude of expenditure can outpatient and former-patient programs be sufficiently extended outside the mental hospital, into the community. It is self-evident that the states for the most part have defaulted on adequate treatment for the mentally ill, and have consistently done so for a century. It is likewise evident that the states cannot afford the kind of money needed to catch up with modern standards of care without revolutionary changes in their tax structure.

Therefore, we recommend that the states and the federal government work toward a time when a share of the cost of state and local mental patient services will be borne by the federal government, over and above the present and future program of federal grants-in-aid for research and training. The simple and sufficient reason for this recommendation is that under present tax structure only the federal government has the financial resources needed to overcome the lag and to achieve a minimum standard of adequacy. The federal government should be prepared to assume a major part of the responsibility for the mentally ill insofar as the states are agreeable to surrendering it.

For convenience, the Veterans' Administration mental hospitals can be taken as financial models of what can be done in the operation of public mental hospitals. *Congress and the National Institute of Mental Health, with the assistance of the intervening administrative branches of government, should develop a federal subsidy program that will encourage states and local governments to emulate the example set by VA mental hospitals.*

Certain principles should be followed in a federal program of matching grants to states for the care of the mentally ill:

The *first principle* is that the federal government on the one side and state and local governments on the other should *share in the costs* of services to the mentally ill.

The *second principle* is that the total federal share should be arrived at in a series of graduated steps over a period of years, the share being determined each year on the basis of state funds spent in a previous year.

The *third principle* is that the grants should be awarded according to *criteria of merit and incentive* to be formulated by an expert advisory committee appointed by the National Institute of Mental Health.

In arriving at a formula, such an expert committee would establish conditions affecting various portions of the available grant, including the following:

1. Bring about any necessary changes in the laws of the state to make professionally acceptable treatment as well as custody a requirement in mental hospitalization, to differentiate between need of treatment and need of institutionalization, and to provide treatment without hospitalization.
2. Bring about any necessary changes in laws of the state to make voluntary admission the preferred method and court commitment the exceptional method of placing patients in a mental hospital or other treatment facilities.
3. Accept any and all persons requiring treatment and/or hospitalization on the same basis as persons holding legal residence within the state.
4. Revise laws of the state governing medical responsibility for the patient to distinguish between administrative responsibility for his welfare and safekeeping and responsibility for professional care of the patient.
5. Institute suitable differentiation between administrative structure and professional personnel requirements for (1) state mental institutions intended primarily as intensive treatment centers (i.e. true hospitals) and (2) facilities for humane and progressive care of various classes of the chronically ill or disabled, among them the aged.
6. Establish state mental health agencies with well defined powers and sufficient authority to assume over-all responsibility for the state's services to the mentally ill, and to coordinate state and local community health services.
7. Make reasonable efforts to operate open mental hospitals as mental health centers, i.e., as a part of an integrated community service with emphasis on outpatient and after-care facilities as well as inpatient services.
8. Establish in selected State mental hospitals and community mental health programs training for mental health workers, ranging in scope, as appropriate, from professional training in psychiatry through all professional and subprofessional levels, including the on-the-job training of attendants and volunteers. Since each mental health center cannot undertake all forms of teaching activity, consideration here must be given to a variety of programs and total effort. States should be required ultimately to spend 2½ percent of State mental patient service funds for training.
9. Establish in selected State mental hospitals and community mental health programs scientific research programs appropriate to the facility, the opportunities for well designed research, and the research talent and experience of staff members. States should be required ultimately to spend 2½ percent of State mental patient service funds for research.
10. Encourage county, town and municipal tax participation in the public mental health services of the State as a means of obtaining Federal funds matched against local mental health appropriations.
11. Agree that no money will be spent to build mental hospitals of more than 1,000 beds, or to add a single patient to mental hospitals presently having 1,000 or more patients.

Our proposal would encourage local responsibility of a degree that has not existed since the State hospital system was founded, while at the same time recognizing that the combined State-local responsibility cannot be fulfilled by the means at hand.

Table 4 provides a hypothetical example of how a Federal-State-local matching program incorporating the suggested merit and incentive features might work. We have assumed for ease of illustration that the States will soon reach an expenditure of $1 billion a year for mental patient care (in 1959 the figure was $854 million). We also have assumed that such a program can induce local tax participation to the extent of $60 million after a 5-year period and $250 million after a 10-year period.

Our proposal is the first one in American history that attempts to encompass the total problem of public support of mental health services and to make minimum standards of adequate care financially possible.

The outstanding characteristics of mental illness as a public health problem are its staggering size, the present limitations in our methods of treatment, and the peculiar nature of mental illness that differentiates its victims from those with any other diseases or disabilities. It would follow that *any national program against mental illness adopted by Congress and the states must be scaled to the size of the problem, imaginative in the course it pursues, and energetic in overcoming both psychological and economic resistances to progress in this direction.* We have sought to acquit our assignment in full recognition of these facts and judgments.

TABLE 4.—*Hypothetical costs to Federal, State, and local governments of doubling expenditures for public mental patient care in 5 years and tripling costs in 10 years under proposed matching plan*

[In billions of dollars]

Year	State expenditure	Federal grants without local participation	Total	Local participation to extent of:	Federal grants for local participation	Grand total
1	1.0	0.1	1.1			1.1
2	1.0	.2	1.2	0.03	0.17	1.4
3	1.0	.3	1.3	.04	.26	1.6
4	1.0	.4	1.4	.05	.35	1.8
5	1.0	.5	1.5	.06	.44	2.0
6	1.0	.6	1.6	.08	.52	2.2
7	1.0	.7	1.7	.10	.60	2.4
8	1.0	.8	1.8	.15	.65	2.6
9	1.0	.9	1.9	.20	.70	2.8
10	1.0	1.0	2.0	.25	.75	3.0

NOTES ON IMPLEMENTATION

The function of the Joint Commission has been that of a study group. We have made a study and from it drawn recommendations for a national mental health program. This completes our job.

It is easy, however, to visualize the next two steps, and even a third. The first is the formation of public opinion for or against the program we propose. The second is the formation of legislative opinion pro or con. The third, and one which we urge the Congress to take immediately, is the formation of a Committee of Consultants who would concern themselves with standards and requirements for implementation of our program and with the kinds of enabling legislation that will be needed. Eventually, we can see that a comparable expert committee, forming an effective channel of communication between the legislature and the mental health professions, will be needed in every state.

In the matter of establishing priorities as they relate to the broad areas of patient care, recruitment, professional education, and research in mental health, we would sound a note of caution. Solution of the mental health problem can and already does pursue two courses. One course is to make better use of the knowledge and experience in the treatment of mental illness that we already have massed, the knowledge on which the broader concepts of treatment in this report are based. Another course is to intensify the search for new knowledge in the hope of mastering the terrain of unknowns to be traversed, and of finding bypasses or more direct routes resulting in preventive measures or treatment methods that are faster working and better adapted to application.

The question is not which course to pursue more intensively. In medicine, professional services, education, and research move together insofar as they center on or relate to patients. Indeed, it is impossible to separate the patients who must be cared for from the persons who must be trained to care for them, and it is impossible to separate either patients or professional personnel from the search for new knowledge that is of vital concern to both.

Indeed, we can see only one matter that takes priority over all others in the program we propose and that is to obtain vastly increased sums of money for its support. Without adequate financial resources, we cannot take care of patients, we cannot educate professional personnel for public service, and we cannot pursue the basic knowledge needed for the prevention and cure of mental illness.

ACCEPTANCE OF THE REPORT ON MENTAL ILLNESS AND HEALTH

Dr. Felix. In addition to this, the American Psychiatric Association quite naturally has given careful consideration to the report, and they have published their stand in support of it. The National Association for Mental Health made it the major point of its meeting in Miami and has endorsed it.

The AMA through its board of trustees has shown a deep interest in this report.

Mr. Fogarty. What have they done about it?

Dr. Felix. They are at the present time considering the recommendations of the 150 people who met in September to consider it under the AMA auspices in Chicago. They have now directed that a series of congresses over the country be held to implement the various aspects of the report.

I cannot speak for the AMA, since I am not an officer of the AMA, but I can say what I heard at this meeting from members of the board of trustees, and similar people.

Their instructions to us were: Take a bold new look at what can be done in the light of this report, and don't worry about any other factor except what you think should be done. We want to implement this insofar as it is possible.

Mr. Fogarty. In other words, they haven't found fault with the report, to your knowledge?

Dr. Felix. No, sir.

Mr. Fogarty. I haven't heard of any.

Dr. Felix. No.

Mr. Laird. You seemed to be quite encouraged when I talked to you in Chicago at that meeting.

Dr. Felix. That is right. I saw both Mr. Laird and Mr. Fogarty there. I did say then, and I still say, Mr. Laird, I am very enthusiastic. I feel that perhaps the sun has finally come up and we are in the early morning hours, at least, of a new day in the field of the mentally ill.

In addition to these, this report is being given careful review and consideration by the administration, with a view to coming up with the administration's position.

The President, as you probably know, has directed that the report be considered by several arms of the executive branch. Specifically he has instructed the Secretary of the Department of Health, Education, and Welfare, the Secretary of the Department of Labor, and the Administrator of the Veterans' Administration to consider this and come up with alternative courses of action to be developed.

In the main, the report addresses itself to the problems of manpower and how to meet them, underscores the importance of additional programs of long-term basic research and emphasizes the needs of community services.

Mr. Chairman, the budget before you, I believe, takes a constructive step toward implementing the recommendations of the joint commission. I would especially call your attention to the increase in funds that we have been authorized to request in the field of training, which is one of the great critically short areas.

Thank you, Mr. Chairman. I hope I haven't taken too long.

Mr. FOGARTY. No. I think it is the best report that I have listened to since you have been appearing before this committee, which is a long time now.

Dr. FELIX. It is quite a long time. This is the first year that I have felt I could come up here and talk with enthusiasm and conviction about large strides forward in the States. I have not talked about research and development here because I can't talk about everything. This is such an exciting new development that I have confined myself to this.

Mr. FOGARTY. I think it is the most encouraging report I have heard in the area of mental health. But we have other areas in public health where training is critical .

Dr. FELIX. Yes, sir. I am a public health officer as well as a psychiatrist.

Mr. FOGARTY. I wish that the people making up this budget had given as much consideration to some of these other areas like heart, cancer, neurology, arthritis and so forth, as they did to mental health.

1963 BUDGET PROPOSALS

It may take another commission to get them off the ground, because this budget isn't going to do it.

The appropriation for 1962 is $108,876,000. The request for 1963 is $126,899,000, an increase of $18 million.

Dr. FELIX. Yes, sir; $18,023,000.

Mr. FOGARTY. This is a pretty good increase compared to the other Institutes.

Dr. Felix, didn't I read in the paper a short time ago that a couple of national voluntary groups have merged in this field of mental health?

Dr. FELIX. That is correct, sir. The National Association for Mental Health and the National Organization for Mentally Ill Children have merged. This will, I believe, strengthen both associations and make it possible to develop a concerted attack at the citizens' level and through the communities on these problems.

ADMINISTRATIVE RESERVE

Mr. FOGARTY. Your reserve is $5,371,000. How much of that is for forced savings?

Mr. VAN STADEN. All but $137,000.

Dr. FELIX. All but $137,000—or $5,234,000.

Mr. FOGARTY. This is something I can't understand about this budget. Here we have this report that is acclaimed by everyone—the President and everybody else. And the President has given you and the HEW and the Labor Department and the Veterans Administrator specific instructions to review the report and come up with recommendations. Here you are being cut back by the same department over $5 million.

Will you supply for the record just how this cut is to be applied?

Dr. FELIX. I will be glad to; yes, sir.

(The requested information follows:)

1962 administrative reserve by activity

[In thousands]

Grants:	
Research:	
Core programs	$1, 226
Clinical research centers	2, 000
Total research	3, 226
Fellowships	1, 548
Training	200
Subtotal grants	4, 974
Direct operations:	
Research	109
Review and approval of grants	141
Administration	10
Subtotal direct operations	260
Total	5, 234

Mr. FOGARTY. Is there any doubt in your mind that if we can prevail upon the Secretary and the Bureau of the Budget to release these funds that this $5 million could be used?

Dr. FELIX. No, sir; it could be used if that were the decision, and assuming that one had flexibility among the various budget activities.

Mr. FOGARTY. If we can prevail upon the Secretary and the Bureau of the Budget to release these funds they can be used to advantage?

Dr. FELIX. Yes, sir; they can be used.

Mr. FOGARTY. They could be used to advantage?

Dr. FELIX. They could be used to advantage; yes, sir.

Mr. FOGARTY. Is there any question in your mind that, if they were released, it would yield substantial returns in the national interest?

Dr. FELIX. No, sir; it would.

BACKLOG IN GRANTS

Mr. FOGARTY. Are you able to finance all approved research applications? 1962, I am talking about now.

Dr. FELIX. No, sir; we cannot.

Mr. FOGARTY. You are $202,000 short?

Dr. FELIX. That is correct.

Mr. FOGARTY. Do you have requests for funds for training programs that you can't finance?

Dr. FELIX. Yes, sir.

Mr. FOGARTY. Would you supply for the record a list of them and the amounts?

Dr. **Felix**. I will be happy to; yes, sir.

Mr. **Fogarty**. There is still a shortage of trained people in this field.

Dr. **Felix**. Yes, sir. This is the most critical area at the moment. I think it should be said here that the administration has recognized this in the budget.

Mr. **Fogarty**. They didn't pay much attention to that in the present fiscal year, though, when they cut you more than $5 million.

(The requested information follows:)

In 1962, a total of almost $44 million in mental health training grant requests was recommended for approval by the Training Committee. This includes approximately $1,400,000 required to pay 8 percent indirect costs on trainee stipends, in accord with a policy adopted in the mental health training program this year. With an available allocation of $34,656,000, this means slightly under $9,400,000 in approved training grant requests will not have been paid in 1962.

Mr. **Fogarty**. Is there unused potential for training that could be used if funds were available?

Dr. **Felix**. Yes, sir.

Mr. **Fogarty**. About half of your increase—$11,689,000—is in research grants; but you still won't be able to finance all approved applications.

Dr. **Felix**. No, sir; that is correct.

Mr. **Fogarty**. According to the table which has been supplied to the committee, you expect to have 214 grants totaling $5,557,000 in 1963 that you will not be able to finance.

Dr. **Felix**. That is correct, yes, sir.

INCREASE FOR TRAINING

Mr. **Fogarty**. So this budget doesn't look as good as I thought it did on the surface. Most of the rest of your increase—$9,994,000—is for training. Am I correctly informed that your Institute is the only one where an increase for training was granted? Maybe you don't know, but Dr. Shannon could answer that.

Dr. **Shannon**. That is correct, sir.

Mr. **Laird**. You can't tell what will happen, though, Mr. Chairman, with the forced reserves for 1963.

Mr. **Fogarty**. If that happens, I think it would wreck the program. If you get this increase you are requesting, will it take care of all the training needs in this field?

Dr. **Felix**. No, sir.

Mr. **Fogarty**. Will you supply for the record why it won't?

Dr. **Felix**. Yes, sir.

(The requested information follows:)

In 1963, a total of $53 million would be required to take care of all needs in the training programs. This includes $50 million to provide for the expansion within the existing program, plus $3 million for the initiation of newer training programs for personnel in the subprofessional and technical areas as well as for the support of inservice training programs for professional and subprofessional personnel.

FELLOWSHIPS

Mr. **Fogarty**. Do you have any increase for fellowships?

Dr. **Felix**. No, sir.

Mr. FOGARTY. Could you profitably use more money in this area if you had it?

Dr. FELIX. If I did not have to concern myself with other obligations of the Government, things which are beyond my power to judge, my answer would be "Yes, I could use more."

Mr. FOGARTY. Supply a statement on that for the record.

(The statement follows:)

RESEARCH FELLOWSHIPS

In terms of need, it is estimated that $7 million could be used in 1963 in the support of approvable research fellowship applications at the following levels:

Predoctoral	$3,150,000
Postdoctoral	1,250,000
Special	750,000
Research career awards	1,850,000

The research fellowship activity provides the primary Institute mechanism for the training of scientific personnel in the mental-health field. The funds provided through this activity are essential in order to attract talented young people to research careers in the scientific disciplines relevant to mental health. They provide a range of fellowship support levels including predoctoral, postdoctoral, and career awards.

In order to meet national needs in the field of mental-health research manpower, additional efforts are deemed necessary in 1963 and future years to provide increased emphasis to training at the predoctoral level, to provide expanded support at postdoctoral level, and to provide, through research career awards, for (1) a greater number of intermediate awards for talented young scientists who have shown exceptional promise in terms of career development and (2) a greater number of long-term awards for experienced researchers in terms of stable career opportunities in mental-health research and academic medicine.

CLEARINGHOUSE FOR MENTAL HEALTH INFORMATION

Mr. FOGARTY. Last year in our report we said we thought you should expand the dissemination of information regarding new developments in the care and treatment of patients. We also recommended the strengthening of the program for psychiatric training of general practitioners.

What have you done? Take the first one first.

Dr. FELIX. We have expanded our publications and reports office to take on some additional people and are now recruiting for some others, which will make possible more rapid communication of research findings to appropriate consumers.

We also had discussions with the people in the States. We are now, and it is one of the recommendations in the Governors' report, in the process of making the first steps in setting up a national clearinghouse for information which will give information in the area of research findings, administrative practices, all of this sort of thing, to all of the States and the localities.

This is not in this budget because we were not ready yet to even submit estimates. But we are well along with this.

Mr. FOGARTY. You don't know yet how much you could use in 1963?

Dr. FELIX. Yes, sir; I do know. If I give you this figure, this is no one's fault but mine that it is not in here because I have not given this to anyone.

Mr. FOGARTY. I am asking you.

Dr. **Felix.** To make our first steps in the setting up of this clearinghouse, we could use about $500,000 next year because we expect to go to electronic methods of storage and the retrieval of information of a lot of material. It will not be a cheap operation.

DISSEMINATION OF INFORMATION

Mr. **Fogarty.** Do you have any better plans than the other Institutes in getting information to the practitioners?

Dr. **Felix.** I can't speak for the other Institutes, Mr. Chairman. I suspect that they are equally able to mount something like this. We have been spending almost the full time of a senior member of our staff with such associates as he needs now for about 6 months going into how to collect this information, how to store it, and how to disseminate it.

We are thinking, for instance, of the possibility of such things as some sort of a periodical information bulletin which would go out to physicians, to nurses, social workers, to hospitals, to State commissioners—people of this kind.

Mr. **Fogarty.** This is an area that should be given a lot of attention, I mean in all fields of health, not only yours.

Dr. **Felix.** That is correct.

Mr. **Fogarty.** Maybe especially yours, because of the advances that have been made in the last 3 or 4 years.

Dr. **Felix.** Things are moving so very rapidly in our field that we felt we could not wait any longer. Dr. Shannon is probably better able than I to give you an exact figure but it seems to me it is something in the neighborhood of about a 2-year lag between the preparation of scientific manuscripts and their publication and dissemination to the people.

Mr. **Fogarty.** Dr. Shannon, will you prepare for the record a report on how much it would take for every Institute to do a better job in this area of getting information to the practitioner more quickly than we are doing now. We are not doing a good job at all. A lot of people have been talking about this problem for 15 years to my knowledge.

We really don't have a program yet.

Dr. **Shannon.** Mr. Chairman, I would like to comment on the particularly good opportunity for establishing a clearinghouse in the National Institute of Mental Health.

Mental Health is one segment of public health in which all the activities of the Public Health Service are concentrated under one administrative supervision.

For this reason the Director of the Institute can address himself to the totality of information in the area from the acquisition and the distribution of research information down to public education.

NEED FOR PUBLIC RECOGNITION OF THE PROBLEM

I would like to comment on this problem of public education, which to my mind is as important as the dissemination of research findings. I have been impressed by the increase in the effectiveness of public information in this field during the past 2 or 3 years.

I think Dr. Felix can tell the committee who has been responsible for this. But my understanding is that it is largely the voluntary agencies who are using such information as is available from the official agencies.

Through the use of radio and television, magazines and other media, the American people are finally being persuaded to face up to the very real problem in a very realistic way.

Mr. FOGARTY. I think it is about time. I remember Mr. Keefe talking about this, and that goes back quite a few years now.

Dr. FELIX. Yes, sir. Mr. Keefe—and you may remember also Mr. Jensen of Iowa when he was on this committee.

Mr. FOGARTY. Yes, he talked about it, too. So we have been talking a lot about it and not doing much. That is why I would like to get these dollar figures put in the record and see if we can't help.

Dr. FELIX. As Dr. Shannon has said, the information to date has been gathered through a combination of the joining of forces of the American Psychiatric Association and the National Association for Mental Health, which puts out a bulletin called Joint Information Service.

It is limited, and they know it is limited. They have both requested us to consider seriously the development of such a service, and they would be very happy to collaborate with us. But the kind of thing that is needed would be completely overwhelming. They couldn't do it within their budget or within their ability to gather the information.

Mr. FOGARTY. Also if you can, when you supply this cost figure, get up a statement projecting how much you think would be saved if you could get this program operating on a good basis.

What would happen if we cut the lag down by from a year to 6 months? What would the amount of the savings be?

Dr. FELIX. Yes, sir, we will supply that.

(The requested information follows:)

CLEARINGHOUSE FOR MENTAL HEALTH INFORMATION

For a considerable period the National Institute of Mental Health, together with outside agencies, has felt the need for the organization and maintenance of a clearinghouse on mental health information for the improved services and coordination of efforts of the NIMH with the States, localities, professional and voluntary organizations, universities, and private individuals concerned with this field.

The proposed clearinghouse would (1) establish an efficient system and national focus for data compilation, and the rapid interchange, storage, documentation, and retrieval of mental health information; (2) maintain an exchange of information with States, professional organizations, voluntary groups, and universities; (3) develop and supply specialized information to the scientific community, lay groups, and the Institute staff; and (4) serve as a national repository and referral focal point of comprehensive information pertaining to all aspects of mental health, particularly in the United States.

Presently large blocks of staff time and tremendous financial expenditures, estimated in excess of $1.7 billion per year, go into the research effort, the training of personnel, and the services to and care of mental patients. Without an adequate means of exchange of information among the 50 States, the professions, universities, and voluntary organizations working in this field, it is apparent that numerous reasons exist for assuming that millions of dollars are wasted each year with less than optimal services to patients through such circumstances as the use of outmoded techniques and practices, the lack of adequate communication between the scientific community and between it and the lay citizenry, and the maximum deployment and use of staff and other available resources.

There exists at the present time a lag in the efficient demonstration of useful techniques through publication of from 1 year to 1½ years. In some cases the publication time has exceeded 2 years. With such a system the time lag or gap between the research findings and their publication could be reduced through cooperative endeavors of voluntary agencies, professional agencies and the Government, to between 4 and 6 months.

As measured against the presently uncoordinated efforts and gaps in information, it may be anticipated that through an efficient clearinghouse, vast savings might be achieved both in financial terms and in the more effective utilization of personnel and other resources. Such savings might be measured in the more rapid application of knowledge from the bench scientists to the practitioner in the prevention of mental illness and in the care and rehabilitation of the mentally ill; and in the proportionate reduced need for institutional and other forms of care of patients on the one hand, and their early return to productive and independent lives on the other.

To the extent that demonstrations of promising approaches to the prevention or control of mental illness can be replicated and undertaken under varying conditions with the results disseminated on as wide a base as possible it may be assumed that savings of hundreds of thousands of dollars may be realized on a minimal basis. A similar circumstance exists to the extent that scientists and practitioners can exchange information and experiences from their own and related fields as rapidly as these experiences have been tested and demonstrated to be effective. Savings of thousands of dollars also may be realized to the extent that supportive personnel are able to apply the numerous emerging techniques and methods by which their resources and those of their communities might best be brought to bear in meeting the problems.

In aggregate the potential savings that can be effected across the Nation may be measured in all of the dimensions of mental illness, as manifested through the changing trends and newer developments in the treatment and care of the mentally ill, and in the innovations in the use of all available resources for the development of comprehensive community and State programs.

Through the more widespread application of the many developments and practices which an efficient system of exchange of information among all relevant groups would make possible, it would appear that a minimum estimate of from $3 million to $5 million in savings per year would not be unreasonable.

In concept the proposed Clearinghouse on Mental Health Information would assist in meeting the foregoing needs, thereby to effect economies in the dissemination of knowledge, in the inculcation of research findings into practice, and in the unification of efforts among all levels of government in cooperation with the scientific and professional community and the lay public.

PSYCHIATRIC TRAINING OF GENERAL PRACTITIONERS

Dr. Felix. You asked also, Mr. Chairman, about the training of general practitioners.

Mr. Fogarty. Yes.

Dr. Felix. This is an exciting thing.

Mr. Fogarty. Is it as popular as we were led to believe in the last couple of years?

Dr. Felix. It is increasingly popular. It has taken a very interesting turn.

Mr. Fogarty. The first year it was slow in getting going, wasn't it?

Dr. Felix. That is correct.

Mr. Fogarty. Then in the latter part of that first year it started to catch on, as I remember it.

Dr. Felix. That is correct. You may remember the way the Congress directed us to begin this. It was divided into two parts. One was the training of the physicians other than psychiatrists in what they needed to know better for general practice.

The other was to provide full psychiatric training for physicians who wished to go into psychiatry.

In fiscal year 1959 there were 94 physicians who entered psychiatric residencies. There were 1,500 physicians who took the shorter courses. In 1960 the residency number increased to 185, and the short-term courses were 1,700.

In 1961 the residencies increased to 304, and people taking the short-term courses to 2,500.

Our estimate for 1962 is that there will be about 340 to 345 residencies, and around 3,000 taking these short-term courses. Our projection within the budget for 1963 is about 375 to 380 residencies, and about 3,200 or 3,300 in the short-term courses.

SHORT COURSES

I said there has been an interesting development. We find now that a number of these physicians say, "What we have been getting in these short-term courses, a week or two, is just enough to make us feel that there is more we need to know. We don't want to be psychiatrists, but we need to know more."

So we are now moving toward and will probably implement in the next fiscal year longer short-term courses, 3 to 6 months' courses, for those physicians who are not going to be psychiatrists, but to give them enough so they can actually treat many of these patients as part of their regular practice.

Mr. Fogarty. Is there a demand for this lengthening of the period of training.

Dr. Felix. Yes, sir. We have gotten it from the Academy of General Practice. We have gotten it from two or three other of the professional organizations.

REQUEST COMPARED WITH FUNDS AVAILABLE IN 1962

Mr. Forgarty. Will you give us a comparison between the money available in 1962 and the requests, and also the same sort of table for 1963.

Dr. Felix. May I supply that for the record? I don't have the table right here. Yes, we will be glad to.

(The requested information follows:)

In 1962, total requests in the general practitioner program amounted to $7 million. Of this total, $4,800,000 will be awarded. Requests for 1963 are estimated at $8 million. In terms of the President's budget it is anticipated that $5,500,000 would be used for awards in the general practitioner program.

NEED FOR EXPANDED PSYCHIATRIC CARE

Dr. Felix. I have felt, and the Joint Commission Report sustains my opinion here, as does the American Psychiatric Association and other groups, that we are never going to get on top of many of the aspects of this mental health problem until many more different kinds of people are treating, actually taking care of—as far as they are able within their abilities—many of the different kinds of emotional disturbances.

The most logical place to turn for this is the physician, the family physician, the surgeon, the obstetrician, the pediatrician, whoever it may be. So it is, we feel, essential that these people be given sufficient training so that they can deal with many of the less complicated types of emotional disturbances which occur in their practice without having to refer them to a psychiatrist.

First, this is a break in the doctor-patient relationship; second, the psychiatrists are overloaded now—they have long waiting lists. We are convinced of this, because as people have become more and more aware of what they can get through psychiatric care and treatment, there has been an increasing demand for it.

This is reflected at all levels—in the hospital area, for instance. As people have realized that hospitals are a place where they can be treated and get well—not a place to go because it is the end of the road—we see these dramatic increases in admissions to hospitals, and a dramatic, even greater, increase in releases from the hospitals.

VOLUNTARY TREATMENT

This is why we see over 26 percent of our admissions to hospitals are now voluntary because there is no longer this dread. As we are able to supply this demand, we will see people coming into treatment much earlier at the first symptoms.

Mr. FOGARTY. What do you think the reasons for these voluntary actions are? Do you think it is because of the improvement in State institututions, or do you think it is because of the growing recognition that there is nothing wrong in having a psychiatric ward in a general hospital?

Dr. FELIX. I think it is some of each. I think it is a better understanding by the public, due to good public education, that there is nothing wrong with having a psychiatric illness. That is, there is nothing terrible about having a psychiatric illness. This is something that can be treated and in many cases cured.

As this idea began to develop, and with the development of the drugs which made it possible to handle many more different patients in settings where they couldn't formerly be handled, we found the general hospitals beginning to accept patients of this kind.

INCREASED NUMBER OF HOSPITALS TREATING PSYCHIATRIC PATIENTS

There are over 400 general hospitals in the United States now who take psychiatric patients, as they would take any other kind of patients.

Mr. FOGARTY. Is that working out?

Dr. FELIX. Yes, sir. I am hoping that we will see this number radically increased in the not too distant future.

I have said, and I may be partly responsible for the actual figure in the joint commission report—although I was not a part of the joint commission—but I have been on record for years, not only here but in speeches over the country, that any hospital of 100 beds or more which did not provide for the care and treatment of psychiatric patients was not entitled to be called a general hospital. It is a specialized hospital.

As long as half the patients in hospitals are psychiatric patients, a hospital that will exclude a group which constitutes half of the total hospital patients in the country surely can't be called a general hospital.

But we have been hammering away at this. More and more of the hospital administrators now recognize that these patients can be treated just as well as any other kind of patients and they are changing their policies.

Mr. FOGARTY. You still have some old-line administrators who don't go along with you.

Dr. FELIX. Oh, yes.

Mr. FOGARTY. I know of some who just don't believe in it. But maybe they have been administrators too long.

TREATMENT FOR ALCOHOLISM

Dr. FELIX. Maybe they ought to go back for a refresher course or something. We are even seeing acute alcoholics treated in general hospitals. We have a contract on a demonstration basis with the Prince Georges Health Department which utilizes inpatient facilities of the county hospital which is on the edge of Washington. They are admitting limited numbers—I don't think they take more than 30 or 40 at a time—of acute alcoholic patients into their general hospital and treat them successfully.

Mr. FOGARTY. What do you mean by treating them successfully? You mean they have been cured?

Dr. FELIX. In the first place, they get them sober and under a prolonged treatment regime. What I meant by treating them successfully was that they didn't create a disturbance on the wards and disrupt the place so they had to take them out of there and put them in a psychiatric ward or psychiatric institution.

You remember perhaps that I reported last year on a new substance which is a derivative of the thyroid hormone which, if injected intravenously into alcoholics, will cause a radical reduction of their blood alcohol so that within 2 or 3 hours the patient is sober enough for treatment and the smell of alcohol has left his breath, whereas when he came in he was comatose and could not give a history.

It increases the metabolism of alcohol. With something like this, you can get a patient down to where he is as manageable as anybody else. He is shaky and sick, but he is sick other than being disturbed.

Mr. FOGARTY. Will that encourage the use of alcohol?

Dr. FELIX. I wouldn't think so, sir. From what I have seen of the patients who have been on such a debauch and have had this treatment, there is nothing attractive about the aftereffects.

Mr. FOGARTY. I was going to ask, What is the reaction to such treatment by the individual? They have something that they take, don't they, which makes them violently sick if they take a drink?

Dr. FELIX. Yes—antabuse. You are thinking of antabuse, I suspect.

Mr. FOGARTY. That hasn't worked out too well, has it?

Dr. FELIX. It has been reasonably effective, but it is not the most desirable thing if we can find something better. What it does is really condition the patient so he has to say to himself: "Do I want to have a drink and then be violently sick, or do I want not to have a drink and not be violently sick?"

If the pressure builds up too much, they may go ahead and have a drink and be violently sick. This substance that we are using now——

Mr. Fogarty. How does this affect the alcoholic, this new substance?

Dr. Felix. It radically increases the rate of metabolism of alcohol in the blood. It almost doubles its rate of metabolism. So the alcohol is broken down to water and carbon dioxide and some other by-products much more rapidly. As the blood alcohol drops, then the centers in the brain are no longer bathed in a solution of alcohol, which is what happens. So the brain then functions normally and the person is sober.

He is sober to the point that you can't even smell alcohol on his breath after 2 or 3 hours.

Mr. Fogarty. How does that affect the habit?

Dr. Felix. In and of itself, I have no reason to believe that it cures the habit. But it does shorten dramatically this particular phase of it and makes the patient more quickly available to other types of therapy, whether it be Alcoholics Anonymous, psychotherapy, or other types of rehabilitative therapy.

Mr. Fogarty. Is there anything else you want to say on this problem of alcoholism? What are we going to spend this year on alcoholism?

Dr. Felix. In fiscal year 1962 our estimates are that we will spend $2,800,000—of which $2,300,000 will be spent in research.

Mr. Fogarty. So we are making some progress. It was this committee which earmarked funds for this problem 4 or 5 years ago, and I think we started out with around $700,000, wasn't it, or something like that?

Dr. Felix. I think that is correct. You would be interested to know, perhaps, that last year we expended $1,700,000. So we are going up this year in our estimates about $1,100,000 over last year.

(The following report was submitted at the request of the committee:)

SPECIAL REPORT ON ALCOHOLISM

INTRODUCTION

The National Institute of Mental Health's program in the field of alcoholism is designed to meet certain immediate needs and to provide a broad, firm base for expanding activity. The specific needs which are being met are concerned with increasing research activities and training programs, attracting competent scientific personnel to the field, and evaluating the current state of knowledge. Concomitantly, consultation and technical assistance services are provided to the several States and interested professional and lay groups.

Alcoholism is viewed by the Institute as a reaction to a series of stressful situations generated by a dynamic and complex interaction of physical, psychological, and social factors. The extent to which each of these factors contribute to the alcoholism syndrome is not now known. While the development of effective treatment and prevention techniques does not necessarily have to await the determination of the specific etiology of alcoholism, such determination will aid in reducing its incidence and prevalence. The Institute's program is, therefore, planned to acquire knowledge pertaining to the relationships among the physical, psychological, and social factors.

PROGRAM DEVELOPMENT

During the past several years, four projects especially germane to the Institute's program in the field of alcoholism were initiated. Prior to that time little systematic work in this area had been undertaken by the Institute. While these projects vary in content and method, the common underlying purposes are to clarify and evaluate existing knowledge and to provide a broad understanding of drinking behavior so that ultimately effective intervention and prevention techniques may be developed. Since these projects are currently underway, no conclusions or results can be presented at this time. However, a brief review and statement of current activities are possible.

Cooperative Commission on the Study of Alcoholism.—The recently formed Cooperative Commission was the result of the combined efforts of Institute staff members and the North American Association of Alcoholism Programs (NAAAP), an organization of State and provincial alcoholism program administrators. While the NAAAP and NIMH were instrumental in its foundation, the Commission is an independent organization supported in part by a grant from the Institute.

The major tasks of the Cooperative Commission, under the direction of a scientific director, are: (1) to make a comprehensive study of such scientific knowledge as now relates to alcohol use and alcoholism; (2) to inventory, study, and evaluate activities, programs, and resources now playing a significant part in attempts to solve or control the problems of alcoholism; (3) to investigate relationships between alcoholism organizations and other resources such as those in the fields of mental health, tuberculosis control, correction, and professional schools for the training of treatment and research personnel; (4) to use the results of these studies to formulate policies and recommendations for improving treatment, education and prevention; and (5) to identify in broad terms what further research is urgently needed.

Dr. Robert Straus, chairman, Department of Behavioral Science, School of Medicine, University of Kentucky, is chairman of the commission, and Dr. Nevitt Sanford, professor of psychology, Stanford University, is the scientific director There are 20 commission members, representing diverse but related scientific disciplines. Dr. E. M. Jellinek, former director for the Yale Center of Alcohol Studies and consultant to WHO, has recently joined the commission's staff and will function as a special consultant for a period of a year.

Alcohol usage patterns.—The first phase of this project, during which techniques and methods for eliciting reliable information about nonpathological alcohol consumption have been developed, is nearly completed. It is anticipated that the second phase will include a national study of the use of alcohol to provide adequate baseline data against which a determination of the extent of deviant alcohol consumption may be made. Currently, the project is located in the division of alcoholic rehabilitation of the California State Department of Public Health.

Influence of sociocultural factors.—This project deals with the influences of social factors on drinking behavior and the occurrence of alcoholism. In one Colorado community three ethnic groups are being studied to determine the various ways in which cultural factors predispose toward alcoholism and the various ways in which the groups cope with the alcoholic. Alcoholism, however, is only one of several forms of deviant behavior which are being studied.

Nomenclature.—One of the hindrances to the advancement of understanding in the field of alcoholism has been the confusing manner in which the terminology in the field has been used. The purpose of this project is to clarify the meanings of key terms and concepts and in the process to build a precise vocabulary to be used for both research and clinical purposes.

RESEARCH

So far as we know, not one etiological factor causes alcoholism. Investigations are being supported, therefore, in many areas of research, ranging from basic biochemical studies to those involving complex social relationships. They include the following: The relationships between adrenal gland activity and alcohol intoxication, the metabolism of alcohol, and the effects of alcohol on the central nervous system; the effects of alcohol on personality; the effects of alcohol on the mental processes; and investigations of auditory and visual hallucinations produced in acute alcoholic psychosis; finally, in the sociocultural areas there are investigations pertaining to the relationship between adult drinking patterns and the socialization process, to the variations in prealcoholic drinking among three nations, and to the orientations of wives toward their husbands' alcoholism.

The Institute also provides support for determining the effectiveness of various forms of treatment. Included are investigations of drug therapy for depressed and schizoid alcoholics, of the effects of initial therapeutic contact, and of the ways in which hospital treatment programs can be continued through referral to community agencies.

In addition to these examples of investigations directly related to alcoholism, there are many research projects which indirectly relate to this problem. Support in the basic disciplines, e.g., physiology, psychiatry, psychology, and sociology, as well as those pertaining to mental health problems in industry, may eventually lead to a greater understanding and control of alcoholism.

TRAINING

Support of training in alcoholism is maintained as an integral part of the general training program in psychiatry, psychology, social work, and nursing. In addition, however, two training grants have been made specifically in the area of alcoholism. One of these is designed to prepare students in casework, who will become familiar with the treatment and rehabilitation problems associated with alcoholism and also to prepare persons with community organization skills to aid in the State programs as well as public health education and volunteer activities. The second grant is a pilot project designed to train social scientists in the area of alcoholism. The trainees are predoctoral students who will engage in seminars and research activities focused on alcoholism. Parts of other grants are concerned with the training of general practitioners and residents, since the medical profession is in a key position to promote community interests and understanding of the alcoholism problem.

While not solely concerned with training, a grant has been made to Rutgers University, New Jersey, to aid in the transfer of the center for alcohol studies from Yale University to Rutgers. The grant will also enable this well-known center to expand its research, education, and publication activities. The center has made significant contributions to the field and its continued existence should do much to advance the understanding of alcoholism.

PROFESSIONAL AND TECHNICAL ASSISTANCE

Technical assistance and consultation services were provided State and local agencies by central and regional office personnel. Assistance is also provided States through technical assistance projects (TAP's). These workshops or conferences which are held in a specific State on a particular problem effectively strengthen alcoholism programs by bringing to people working on State problems expert knowledge in the problem area. Four TAP's were held in 1961: Planning agency participation in a State alcoholism program (South Dakota); nursing care for the alcoholic in the general hospital setting (Massachusetts): education about alcohol (Kansas): and developing an effective alcohol education program in the public schools (Georgia).

In Prince Georges County (Md.), a collaborative project sponsored by the Institute's Mental Health Study Center and the Prince Georges County Health Department is in its third year. This project was initiated to determine the ways in which community resources might be used most effectively in rehalibitating the alcoholic and aiding his or her family, to explore ways in which educational and preventive measures might be undertaken, and to evaluate the efforts being made to assist the alcoholic. Recently a cooperative relationship has been established with the Spring Grove State Hospital, so that every alcoholic patient discharged from the mental hospital who is a resident of Prince Georges County is followed up systematically by the county clinic's staff. The significance of this project lies in its effort to mobilize all the county's resources to aid the alcoholic: the evaluation phase, when completed, should provide a measure of the effectiveness of this approach.

During the past 2 years, Institute staff members have been working closely with the Division of Accident Prevention, BSS, PHS, in the field of drinking and driving. A national conference on this topic was held in 1961. Representatives from law enforcement agencies, public health departments, the judiciary, legal profession, psychology, physiology, sociology, and other related disciplines attended. There has been a great demand for the papers presented at the conference; and two half-hour educational television shows are being prepared on this subject.

Consultation to the several States continues as new State programs are initiated and others modified. For example, in Illinois and Indiana, State departments of mental health, each including a division of alcoholism, were established. Kentucky created a division of alcoholism in the State department of health, while New York created a similar division in the State department of mental hygiene. Maryland and Iowa established commissions on alcoholism. These various State activities reflect a growing awareness of the problems associated with alcoholism and the fact that the several States are planning to deal more effectively with them.

SUMMARY

Alcoholism is a complex problem which has physical, psychological and social facets. It is essential, therefore, that investigation of these facets, both separately and in combination, be supported. It is essential, too, that a broad base of knowledge about drinking behavior and alcoholism be established if effective control and preventive measures are to be instigated.

The establishment of the independent Cooperative Commission on the Study of Alcoholism will provide for a systematic review of what is known and what needs to be known about alcoholism. Many of the problems in the field will be brought under scientific scrutiny and can be attacked in a coordinated manner. However, the difficulties resulting from the shortage of scientific personnel, of inadequate and inaccurate knowledge, and of generally low prestige of the field remain. The Institute's program is designed to aid in overcoming these substantial problems.

Funds obligated for the various alcohol programs for the year 1959–63:

Year	*Research grants*	*Training grants*	*Total*
1959	$870, 927	$5, 200	$876, 127
1960	1, 068, 516	------	1, 068, 516
1961	1, 262, 954	------	1, 262, 954
1962	2, 300, 000 (*est.*)	58, 019	2, 358, 019
1963	2, 800, 000 (*est.*)	25, 803	2, 825, 803
Total	8, 302, 397	89, 022	8, 391, 419

JUVENILE DELINQUENCY

Mr. FOGARTY. We also recommend putting greater effort into juvenile delinquency, and the President set up a Presidential Commission about a year ago.

Dr. FELIX. That is right, he did.

Mr. FOGARTY. Has that Advisory Board been named yet?

Dr. FELIX. I believe it has.

Mr. FOGARTY. What are you doing in this field? Are you cooperating with this group?

Dr. FELIX. Yes, sir, we are.

Mr. FOGARTY. They have an authorization of $10 million for 3 years?

Dr. FELIX. I think that is correct.

Mr. FOGARTY. How are you working with them?

Dr. FELIX. One member of my staff is assigned full time to the juvenile delinquency area. He works very closely with Dr. Lloyd E. Ohlin, who is the Special Assistant in the Department of Health, Education, and Welfare on the Secretary's staff, and with Mr. Hackett over in the Department of Justice.

They have a complete exchange of information about what is going on, what kind of projects are coming up, where they would be most properly supported, and so forth.

This fiscal year (1962) we expect to expend in this area about $4,250,000, of which about $3,150,000 will be in research, and about $400,000 will be in the area of training, and about $700,000 will be in the area of State control programs, working with the State agencies and assisting them at the local level.

PROVIDENCE PROGRAM

Mr. FOGARTY. Have you given consideration to attacking this problem through better recreation facilities?

Dr. FELIX. Yes, we have. There are some efforts going to be directed this way, not exclusively recreation, but as part of a larger program.

Mr. FOGARTY. The reason I asked, the city of Providence is going to make a request for a grant from this other appropriation, not yours. They have been fairly succeessful in dealing with this problem through a recreational approach, by going out and getting these problem boys and girls and getting them into a swimming pool or gymnasium or something like that.

They tell me that the old way was let them come to you, but they have changed that. They are going after them.

Dr. FELIX. This is what is called the aggressive approach, going out after them. Incidentally, my staff has prepared briefing documents for me not only in this area but in the others you have mentioned—alcoholism and the others. If you would like, I can submit these.

Mr. FOGARTY. Put that in the record.

Dr. FELIX. Thank you, sir.

(The information referred to follows:)

SPECIAL REPORT OF JUVENILE DELINQUENCY

EXTENT OF THE PROBLEM

Juvenile delinquency is a problem which continues to merit the serious concern of the people of the United States. The number of delinquency cases disposed of by juvenile courts in the United States has risen for 12 consecutive years. In fact, the number of such cases increased by more than three times between 1948 and 1960. And although the child population of delinquency age increased by about a third during this period, the actual delinquency rate per thousand children of delinquency age more than doubled. It is reliably estimated that 1 boy in 5 in this country has a delinquency record by the time he is 18 years old. It can, of course, be argued that many of the offenses that are counted in establishing this figure are relatively minor. This is true, but there are other reasons for regarding the official statistics as indicating only the part of the iceberg that shows above the surface. For example, it is reported by the Children's Bureau that for every child who becomes a juvenile court statistic there are two or three who are dealt with informally by the police even though they may have committed similar offenses. In addition, the Federal Bureau of Investigation indicates that for all reported major crimes in the United States only about 1 in 4 results in an arrest.

But there are other serious considerations. Even if the delinquency rate levels off, the problem will increase by about 50 percent by 1980, since the child population of delinquency age will increase by about 50 percent in the next two decades. In addition, in the next decades many more of the people of the United States will be living in or near big cities. At present the big city delinquency and adult crime rates are at least three to four times the rural and smalltown rates. It seems likely, therefore, that as the Nation becomes more urban the delinquency and adult crime rates will continue to rise.

THE REPORT TO CONGRESS

In view of this situation, in the spring of 1959 the House Appropriations Committee requested the National Institute of Mental Health to collaborate with the Children's Bureau in preparing a comprehensive report for the Congress on juvenile delinquency. The report was submitted in February 1960, and with its appendixes supplies a new source of documentation concerning delinquency.

NEEDED TASKS

When the report was completed, it was apparent that a number of needed tasks must be accomplished if adequate control of the problem is to be achieved. These tasks involve the following areas: (1) Demonstration projects, (2) training projects, (3) broad support of basic and applied research, (4) the development of evaluative research instruments, (5) a research and information center, (6) National, State, and local surveys of delinquents, (7) theory development, (8) collaboration with private effort, and (9) collaboration with other Federal agencies.

(1) *Demonstration projects.*—It is important to determine how effective present knowledge, skills, and resources can be when adequately mobilized to meet the problem. Demonstration projects must be undertaken to attack the problem at various stages of its development. Attention needs to be given to early prevention, to early identification of predelinquents, to effective treatment at the time of the first offense, and finally, to the rehabilitation of the chronic offender.

(2) *Training projects.*—Because of the great shortage of trained personnel in the delinquency field it is important that training projects be inaugurated which develop and test training methods for all types of both professionals and nonprofessionals.

(3) *Broad support of basic and applied research.*—Since research investigation of the delinquency field is only in its beginning stages, it is important that a wide range of research approaches be supported.

(4) *Development of evaluative research instruments.*—Since there are no widely accepted techniques and instruments for evaluation of the effectiveness of delinquency programs there is need for the development of methods by which both small programs aimed at a few individuals and larger programs which attempt to deal with the problem on a citywide basis are evaluated.

(5) *Research and information center.*—Another high priority need is for an information center in which research and service projects in the field can be described, cataloged, and made available to professionals and other interested persons in the field through journals, digests, collections of abstracts, series of monographs, films, etc.

(6) *National, State, and local surveys of delinquents.*—As indicated in the introduction of the report to Congress, national data regarding the extent and nature of the problem is very inadequate at present. When a national rate increase is reported by the Children's Bureau this increase cannot be evaluated in terms of type of offense, proportion of chronic or recidivated delinquency involved, or segments of the juvenile population involved by socioeconomic status, ethnic group, age, family composition, etc. Given the present state of our knowledge, it is difficult to determine how seriously or in what ways such rate increases should be dealt with. If the increase is mainly in the area of minor traffic offenses and the mischievous behavior that is characteristic of adolescents, the problem may not be one of national concern. If, on the other hand, the rate increase consists primarily of the more serious offenses, as it is believed, and represents an increase in the chonic antisocial type of delinquent, the problem becomes very serious indeed, and requires much different control measures.

(7) *Theory development.*—The foregoing needs must be met if the meaning of the problem for the United States is to be evaluated and immediate measures for attacking the problem undertaken. At the same time, however, planning for a more systematic theoretical long-range approach should be initiated. This is required because no experienced person in the delinquency field feels that an adequate understanding exists at present regarding the processes which are involved in the development of the many different types of delinquents existing in our society. It is important, therefore, that mental health and social science theory relating to juvenile delinquency be organized into as coherent a whole as possible and then divided into areas or subunits which are amenable to scientific investigation. Once such areas are identified they can be carefully analyzed by groups of experienced professionals in the field with a view to designing, initiating, and conducting appropriate research and demonstration projects in these areas.

(8) *Collaboration with private agencies.*—It is also important that collaboration with private agencies in the field be sought, since such agencies as the Ford Foundation, the National Council on Crime and Delinquency, the National Council of Juvenile Court Judges, the American Public Welfare Association, and others are actively concerned with the problem.

(9) *Collaboration with other Federal agencies.*—Such collaboration is obviously necessary as a comprehensive Federal attack on the problem is undertaken.

THE CURRENT INSTITUTE DELINQUENCY PROGRAM

Following the submission of the report to Congress, $1 million was earmarked in the 1961 Institute budget and $2.2 million in the 1962 Institute budget for delinquency projects. The 1962 allocation was distributed by the Institute as follows: $1.6 million for demonstration projects, $300,000 for regular research grant projects, and $300,000 for professional training projects. In addition, an effort was made to see to it that the activities listed above, which are deemed necessary for a telling attack on the problem, were carried on effectively. The following accomplishments can be reported at this time.

(1) *Demonstration projects.*—A number of demonstration projects are in operation involving approximately $1,700,000 in 1962 funds. In addition, it is estimated that at least $300,000 in new grants may be approved for payment from 1962 funds before the end of the year.

(2) *Training projects.*—It is estimated that $400,000 will be allocated from 1962 funds. Approximately $650,000 in applications are being reviewed. It is expected that there will be a backlog of $100,000 in projects approved but not awarded in 1962 because of shortage of funds.

(3) *Broad support of basic and applied research.*—Approximately $1 million has been awarded thus far for delinquency research projects in fiscal 1962. It is estimated that another $150,000 more will be awarded for such projects in fiscal 1962.

Thus it is anticipated that during 1962, funds in excess of $3.5 million will be utilized for delinquency projects.

(4) *Development of evaluative research instruments.*—Preliminary reports regarding one large-scale evaluative instrument will be available in the spring of 1962. This project is being developed in New York City and will yield valuable information regarding the extent and nature of the problem.

(5) *Research and information center.*—An NIMH-supported research and information center is now well organized at the National Council on Crime and Delinquency. Here, not only national but worldwide information on research and action projects is being collected and prepared for dissemination. The staff of this center has also given valuable consultation to the President's Committee on Juvenile Delinquency and Youth Crime, and to the staff of the DHEW delinquency program.

(6) *National, State, and local surveys of delinquents.*—Investigations are continuing in three cities preparatory to undertaking a nationwide study of the extent, trends, and nature of delinquency. In addition, NIMH staff members are collaborating with the President's Committee and with the DHEW staff in planning the gathering of national data.

(7) *Theory development.*—In collaboration with the Ford Foundation, NIMH has supported two conferences concerned with theory development and research strategy in the delinquency field. In addition, investigators from several NIMH delinquency projects have been brought together to share concepts, theoretical approaches, and research instruments.

(8) *Collaboration with private agencies.*—As indicated above, active liaison is being maintained with the Ford Foundation and the National Council on Crime and Delinquency. In addition, NIMH has supported a pilot training project sponsored by the National Council of Juvenile Court Judges and the National Training Laboratories, and is considering the possibility of further training support of juvenile court judges. Staff liaison is also maintained with the American Public Welfare Association and the Council on Social Work Education.

(9) *Collaboration with other Federal agencies.*—With the inauguration of the President's Committee and the new grants program in DHEW, considerable collaboration between NIMH staff with the staffs of these programs has been appropriate. It is our impression that a close, effective working relationship has been achieved so that the NIMH delinquency program can perform a substantial and appropriate role in the Government-wide offensive against the delinquency problem.

MENTAL RETARDATION

Mr. **Fogarty.** I have a special interest in the problem of mental retardation. Do you want to mention anything else in addition to what you had in your prepared statement regarding mental retardation?

Dr. **Felix.** In fiscal 1962 our projection is that we would spend about $5,275,000 in the area of mental retardation, of which something over $4 million will be spent in research.

I think it is interesting to note that our program in mental retardation took a sharp upswing in intensity and in funds at the beginning of fiscal year 1956. That was the year that this committee directed that increased funds be spent in this specific area.

There has been a steady increase in this activity since fiscal year 1956. Our expectations in fiscal year 1963 within the budget before you is that we will expend in the area of retardation about $6,375,000.

PHENYLKETONURIA

Mr. **Fogarty.** You mentioned a couple of years ago that we are making some progress. Tell us about the progress with regard to phenylketonuria.

Dr. **Felix.** This is a very fascinating thing.

Mr. **Fogarty.** Have you been able to reduce the time for diagnosis yet?

Dr. **Felix.** It is about 6 weeks. I have seen a report in the last few days that there are a few cases that have occurred later than that. I can't think exactly what the time was. It is something I have seen in the last few days or weeks.

A few cases have appeared after this length of time.

Mr. **Fogarty.** Tell us about this test and what has been accomplished.

Dr. **Felix.** They found that by certain color tests, chemical tests, of the urine in new-born infants—that is, within the first several weeks, beginning at about 2 weeks through the sixth week of life—those children who are going to be PKU children—that is, they are excreting phenylpyruvic acid in their urine—can be detected.

TREATMENT

Once they have been detected, then these children will be put on a diet which contains no phenylalanine, which is the substance which does not break down properly to an amino acid known as tyrosine. But you get this byproduct or this degradation product known as phenylpyreuvic acid which is apparently the toxic substance in these children.

By putting them on the special diet, they have been able—as far as they have been able to go through for about 6 or 7 years, and we think this is conclusive now—to prevent mental retardation.

I don't know if you noticed in Life magazine 2 or 3 weeks ago, but they had a picture of two sisters. I think they were from Denver, if I am not mistaken. The older of the two sisters had not been detected, and she is a profound retardate. The other sister, who is 5 or 6 years old, had been detected early in this first 6 weeks and was a normal child with a normal I.Q., going to school and acting as a normal youngster.

She is off of this special diet.

Mr. Denton. There were pictures of them in the paper.

Dr. Felix. That's right; yes, sir.

Mr. Fogarty. They had their pictures taken with the President and the president of the voluntary organization, Mr. Fitzpatrick.

Dr. Felix. That is right, yes.

DEVELOPMENT OF DETECTION PROCEDURES

Mr. Fogarty. I think that was a very striking example. Suppose this test cannot be given in the hospital because the child has been taken home. Hasn't something been developed where the pediatrician can send some sort of a napkin to the mother and that can be sent back to the laboratory?

Dr. Felix. Now, because of the number of them and all that they are testing, these are usually sent to a central laboratory where they can be rapidly tested.

Mr. Fogarty. Is this well organized? Are the doctors acquainted with this, and are they doing it?

Dr. Felix. Obstetricians and pediatricians particularly are pretty well oriented to this. They are the ones who see these children the most anyway. The Children's Bureau has announced in the last few days the initiation of a nationwide screening program to throw a screen over the entire country to see how many of these are picked up so that they can institute treatment at the earliest possible date.

We were also negotiating before this came out, and have just consumated——

Mr. Fogarty. Before we finish, tell us what happens. The obstetrician or the pediatrician sends what to the family?

Dr. Felix. There are two ways of doing this. In some cases the diaper itself can be sent. In others, there are pieces of specially treated paper which are then analyzed by paper chromatography. They are placed in the diaper. When the child urinates, either the paper is saturated or, if not the paper, the diaper is saturated.

Then these are sent to a central laboratory—in the large cities it is in the same city—and are tested either by paper chromatography or by a ferric chloride color test.

They do this continuously—that is, every day or so—for the first 6 weeks of life in those that are not positive. But once it is positive, they can discontinue it.

The family is immediately notified if the test is positive, and a diet is prescribed which is low in phenylalanine and the child then can develop perfectly normally.

DIET PRESCRIBED FOR AFFECTED CHILDREN

The families who are notified are instructed as to what it means and what they should do about it.

Mr. Fogarty. What kind of a diet is it? Is it a very strict diet? How long must a child stay on the diet?

Dr. Felix. Through about the fifth year. By this time apparently the excretion of this material doesn't make any difference any more. The brain is developed so this cannot exert its deleterious effects.

Yes, it is a strict diet. It is not the nicest diet in the world, but it is an effective diet.

We are working in our laboratories, and there is work going on elsewhere, to try to synthesize and prepare—so that it can be used—the coenzymes of which there are two which are essential to the breaking down and metabolism of phenylalanine and tyrosine.

Once this has been done, then hopefully, instead of giving the child the diet, one can feed the child this particular enzyme and then he can be on a regular diet and will be able to break down this material himself. This would be comparable—I use this as an illustration, though it is not the same—to giving a person insulin, now that we have insulin, which will allow a fuller, richer diet than in the days before insulin was discovered, when they just had to be cut way down on carbohydrates and fats.

Mr. Fogarty. Is there any other progress of significance in this area?

Dr. Felix. I reported in my opening remarks about the day-care clinics for the mentally retarded in various parts of the country.

FINANCING SHELTERED WORKSHOPS FOR RETARDED CHILDREN

Mr. Fogarty. Do you support sheltered workshops?

Dr. Felix. Yes, sir; we do. The Office of Vocational Rehabilitation supports a number of them. We do through our grants to States. There are a number that are supported through our grants also.

There are two ways this may be done. One is that each State, each year, in order to participate in the formula grant money—the grants to States money—must submit a plan and budget for the review and approval of the Surgeon General or the person whom he designates to do this.

We find in a number of States that this is part of their plan and they budget what they are going to use this formula grant money for.

Others have applied through our so-called title V program to set up demonstration units of this kind in order to demonstrate its effectiveness.

Then, following that, they will include it in their own State budget.

We are also negotiating with two or three States at the present time. We are just about ready to or will sign a contract with one within the next few days to put on a statewide demonstration of this—not just a few towns in the State but a statewide demonstration. Hopefully then, after this has been demonstrated, the State will pick it up.

PROVIDENCE PROJECT

Mr. Fogarty. Would it be possible for a sheltered workshop which is receiving funds from the Vocational Rehabilitation Program to secure funds from your appropriation, too, if there is reason to expand? I am thinking of the one in Providence, now. I have seen some dramatic results, with these people working for the first time in their lives; perhaps not earning a living, but at least on a piecework basis they are taking money home every week. But the operation is only big enough to support about 30.

Of the 30, 10 have been taken out of the State institution. So it is a big saving for the institution and now these people are living at home and going to this workshop assembling jewelry or whatever subcontracts they can get from various firms.

If that is working out well there, maybe it should be supported in three or four sections of the State. I was amazed that one-third of the people in this one came out of the State Institution for the Mentally Retarded.

Dr. FELIX. I will have to check to be sure that I am correct as far as the law and regulations are concerned, butI believe that there would be nothing to prevent such a State from applying to us, even though they were receiving grants from the Office of Vocational Rehabilitation.

(NOTE.—It is possible for the Institute and OVR to support separate aspects of the same project.)

Mr. FOGARTY. There was one girl 23 years of age in this shop, and she hadn't been out of the house in 20 years. That may be a more dramatic example than any of the others, but here she is for the first time in 20 years out of the house and taking home some money every week.

Dr. FELIX. It is amazing what they can do. There are several thousand such people in the United States now who are out as a result of this kind of program, and are to some extent up to totally supporting themselves. They are not going to be nuclear physicists, but there are other things needed besides nuclear physicists.

Mr. FOGARTY. Along with this workshop they also have a childcare center. They have facilities for these people in their twenties, I guess would be the average age. It seems to be working out very well.

Mr. FOGARTY. Is there anything else you want to say on this problem?

SPECIAL REPORT ON MENTAL RETARDATION

Dr. FELIX. I will be happy to submit for the record this briefing statement, which is a fairly complete one and that will save you time.

(The information referred to follows:)

INTRODUCTION

The National Institute of Mental Health has been deeply interested and concerned with the problem of mental retardation for several years. The effect of the Institute's activities in this field is indicated by the increase in expenditures from $2,400,000 in 1959 to an estimated $5,275,000 for 1962. This supports a broadly based program of an varied nature as indicated by the following four general areas:

Program development.—Efforts through special projects, consultation, and support of services;

Research.—Contributions to basic knowledge through direct research on the Bethesda campus as well as grant support to investigators throughout the country;

Service.—Improvement and expansion of service programs through demonstration projects, technical assistance and consultation, and grants-in-aid to States;

Personnel.—Increase in the numbers and competency of professionals in the field through support of training both directly to universities and through special projects concentrating on inservice and staff development.

President's Panel on Mental Retardation

The field of mental retardation was given new impetus as a result of the President announcing the formation of a distinguished group of leaders in fields related to mental retardation to "develop a coordinated and comprehensive attack on the problem of mental retardation." This distinguished group, which includes physicians, educators, lawyers, psychologists, social scientists, and leaders in the field is to prescribe a program of action by the end of 1962. The importance of mental retardation as a national problem was clearly indicated—"the large number of people involved * * * the great cost to the Nation * * * the striking need * * * the vast area of the unknown that beckons us to increase research efforts * * * all demand attention."

The problem

Mental retardation is a serious problem affecting many aspects of our society. Over 5 million individuals are estimated to be retarded. The host of problems presented by these people, to themselves, to their families, and to their communities include biological, psychological, educational, vocational, and social areas of concern. Mental retardation must be approached through the whole life cycle, from consideration of genetics and conception, through pregnancy, delivery, childhood, adolescence, adulthood, and old age.

A small proportion of the retarded, estimated at 4 percent of the total (200,000 individuals), are cared for in institutions at an estimated annual cost of over $1¼ billion. A much larger sum of money, for which we have no good estimate, is expended by families and communities for the care, education, and rehabilitation of the retarded.

Describing the problem

The Institute has taken a leading responsibility for accurately defining and describing certain aspects of the problem of mental retardation. Its biometrics program serves continuously as the central point for the collection of data on patients resident in institutions for the mentally retarded. More recently the Institute has succeeded in organizing collection of nationwide data on patients seen in psychiatric clinics. This revealed 26,163 patients with mental retardation who were seen in 1959 in psychiatric outpatient settings. Active planning continues for further development of this vital descriptive analytic work. A substantial part of the 12th Annual Conference of Mental Hospital Statisticians, to be held in Madison, Wis., in 1962 under the sponsorship of the Institute, will be devoted to the discussion of mental retardation. Plans will be formulated for the development of uniform definition among States and the design of meaningful tabulations describing the movement and characteristics of patients in institutions for the mentally retarded comparable to developments which have taken place concerning data on hospitals for the mentally ill.

I. PROGRAM DEVELOPMENT

The National Institute of Mental Health has given general support to the field both by special projects as well as consultation and technical assistance from its own staff.

American Association on Mental Deficiency project on "Technical Planning in Mental Retardation"

A crucial grant of the Institute has played an important role in the general development of the field of mental retardation. In 1955 funds were made available to the professional association in the field, the American Association on Mental Deficiency, for a project entitled, "Technical Planning in Mental Retardation." The basic purpose of this project was seen as the delineation of current needs, the stimulation of creative thinking, integration, and organization of work which had already been done, the improvement of liaison between interested groups and individuals—professional, Government, lay, and parents. For functional and organizational structure the broad general problems were thought to fall into three categories: research, training of personnel, and programing.

The results of this concentrated effort have been significant. They include publication of selected abstracts in the American Journal of Mental Deficiency; a bimonthly newspaper, Project News, disseminated widely throughout the Western World; a 10-year index of the American Journal of Mental Deficiency—a mechanism to increase the exchange of information in the field; a manual on terminology and classification in mental retardation to aid in the difficult fields of standards and criteria; a survey study and report of cooperative relationships established between residential facilities for the mentally retarded and colleges and universities; a review of the status of research in mental retardation due for publication in June 1962; a manual on program development; a study of minimal standards for residential institutions; staff consultant services to various professionals in many areas such as school superintendents, State department officials, sheltered workshop directors, and others; and an analysis of existing State laws governing the retarded.

An important activity of the project has been the calling of key conferences in selected areas crucial to the development of the field. These have included a conference to study how mental retardation as a subject can be introduced into medical schools, how professionals working in the field of rehabilitation can more adequately prepare and place the retarded into suitable employment, how more and better trained psychologists can be included in the field; how social workers can be better trained on graduate levels; how inservice training for attendants in residential institutions can be improved; and what moral, ethical, legal, and human problems are involved in the use of human subjects in research. A symposium on research design and methodology in mental retardation was sponsored jointly by the Woods School and the project. A resulting publication has been useful throughout the field.

As in any project of this nature, many indirect benefits have accrued which are not measurable. Among these are dissemination of new information for large groups and the resulting stimulation to action; the cross-fertilization of ideas among the disciplines; the encouragement of demonstration programs and new research projects; perhaps most important, the rekindling of feelings of security and enthusiasm as well as recognition in individuals and groups who have long been working in isolated units. This project, through Institute support, has presented the most comprehensive attack on the multiple problems in the field of mental retardation today. The full scope of the project's work was made available to the President's panel through the research associate of the technical project becoming the research director of the President's panel.

II. RESEARCH

Intramural

The Institute supports a broad gage program aimed at obtaining new knowledge in many aspects of the field of mental retardation. Research activity takes place at the Bethesda campus through direct research activities. There is activity in the laboratories relevant to crucial biochemical problems such as those involved in phenylketonuria.

The new biosocial growth center is conducting a series of studies of parents and children. Stress is placed on psychological factors and on patterns of neuromuscular behavior in the infant and young child. The Institute is also conducting a basic study of family relationships as they differ in various socioeconomic classes.

Extramural

Support in research activities ranges across the full gamut of the basic dimensions of the field of mental retardation. Research is supported in the biological, educational, psychological, and sociocultural fields. Quantitatively the extent of this support is indicated by the approximately 80 research projects in or immediately related to mental retardation now being supported by the Institute. This constitutes an expenditure of $2.8 million in fiscal year 1961, an estimated $4.1 million in fiscal year 1962, and over $5 million in fiscal year 1963. The qualitative extent of the research attacks will be indicated by a few pertinent remarks on each area.

BIOLOGICAL

Research projects range across the full biochemical spectrum. Studies in the metabolism of fats, protiens, carbohydrates, and other substances including their directly relevant clinical entities such as phenylketonuria, maple sirup urine disease, galactosemia, and others are being intensively pursued. An important and fruitful breakthrough in gaining mastery over disease process is the ability to create its parallel in animals. This has recently been achieved by creating mentally retarded monkeys with phenylketonuria. Attempts are being made to get experimental animals with other diseases of errors of inborn metabolism such as galactosemia. Basic biological developments are being studied in such areas as the Prenatal Development of the Human Cerebral Cortex. Surprising findings which open unexpected roads to new knowledge have already been found. Studies of 8-month and 7-month-old fetal brains have revealed that the number of cells is 2 to 5 times higher than in the newborn. The biological studies extend into the usual clinical entities such as mongolism and cretinism. The most publicized recent breakthrough in basic biological knowledge relative to mental retardation is the discovery of the chromosome abnormality in mongolism. These abnormalities of the chromosomes, the basic stuff of life, are being pursued in several different areas including their relationships to human behavior. Thus basic knowledge is being pursued from genetics, through studies on the clinical disease process itself, with feedback of knowledge from basic science to the clinical laboratory and ultimately to prevention and treatment of the multiple types of mental retardation.

PSYCHOLOGICAL

The complex psychological and psychiatric aspects of mental retardation are being studied in several ways. One such study is of Psychological Development in Cerebral Palsy. Here the focus is on the role of initiative and the increment in psychological development of cerebral palsied children that may take place through an environment that promote initiative as compared with a more routine environment. Other studies are in language development and speech development. Here the focus may be directly on mental retardation or more basically on the actual processes of development themselves. The many handicaps suffered by mentally retarded children serve as research material for vital questions such as the development of speech in deaf children, the development of motor skills in the cerebral palsied.

EDUCATIONAL

A significant amount of activity is being supported in the area of learning and education. These involve basic studies in animals as well as in mental retardates. These studies in the basic learning process merge into studies of the effectiveness of various teaching techniques. These include several projects on experimental use of machine teaching of reading, arithmetic, and other basic subjects in retarded children. The study of reading ability is pursued in several ways including influence of drugs upon this vital skill.

SOCIOCULTURAL

The retardate is a member of the family and the community. Several studies have centered on this aspect. A question frequently asked is: "What is the effect of a mentally retarded child on his brothers, sisters, and parents?" An important investigation, looking directly at this problem, is the study of the Siblings and Parents of a Mentally Retarded Child. This investigation seeks to determine effects of the presence of a severely mentally retarded child upon the relationship between his parents and his normal siblings. It focuses upon aspects of the relationship which appeared to have consequences for the mental health of the intellectually normal sibling of a retarded child.

The broad range and scope of the research effort being supported by the Institute as indicated by studies in such general areas so useful for filling out the basis for understanding the problem of the field as the History of the Problem of Mental Deficiency. Another study is supporting translation and review of the Russian psychiatric literature relative to mental retardation and its rehabilitation techniques.

SERVICE

Development of demonstration, experimental, and pilot projects

Under the program of mental health project grants, the Institute is able to support demonstration, experimental, and pilot studies related to the care, treatment, and rehabilitation of the mentally retarded. Among projects currently being supported, a wide range of patients, both in terms of age and severity of retardation, are being treated in a variety of settings utilizing several professional groups and techniques. More specifically programs now being supported include, Day Hospital Service in a Child Guidance Setting, which serves as a pilot project which will hopefully serve as a guide for further development of day-patient services, a language development program for mentally retarded children, a program for preschool retardates and parents, interdisciplinary investigation of learning disorders, an occupation day center for mentally retarded young adults, use of public health nurses in a retarded children's program, and studies in parent counseling. A promising project is that which will explore in depth the Collaborative Management of the Mentally Retarded. This project is unique because it includes and coordinates the cooperative facilities of a university medical center, the major community resources for education and welfare, and the State facilities within the framework of a teaching hospital.

A recent demonstration program is the counseling and referral service for the mentally retarded in New England. This demonstration of a statewide service is jointly sponsored by the State Council on Community Services and the State Association for the Mentally Retarded. The purpose of the demonstration is to show what an information, referral, and counseling service can do to identify problems of mental retardation, find out why agency services are not available to help families and mentally retarded persons to assess the needs of the community, and to help staff members of health and welfare agencies and other professional groups become more familiar with the problems of mental retardation and more able to give service.

Control programs in phenylketonuria

Intense activity had laid the groundwork for large scale demonstration programs for the control of phenylketonuria. This has included a review of the literature (now ready for publication and distribution throughout the country), study of current State programs, and field visits. As a result of consultation and negotiation with the Institute, several States have submitted programs of various types. Approaches include: A comprehensive screening treatment and followup on a statewide basis; intensive clinical and laboratory studies of the population of a State institution; screening of all children in special classes for the mentally retarded throughout a State.

State programs

Organization changes in several States have given increased recognition to the importance of mental retardation programs. Several States such as New York and New Jersey have set up central offices of mental retardation to help coordinate the multiple approaches necessary to fully meet the problem, including health, education, and welfare. The program of nursery centers for preschool mentally retarded children, operated by the Massachusetts Department of Mental Health, continues to expand. Thirty centers are now in operation over the State. The purpose of the program is to aid in better diagnosis and evaluation of retarded children and to provide therapeutic services and training for future placement of the children in special classes of the public schools. Counseling for parents of the children is also part of the program. Other States have now developed similar nursery services such as those in Delaware.

Federal grant-in-aid funds contribute to a variety of programs which include, for example, support of Minnesota's Social Development Center for the Mentally Retarded. The purpose of this center is to provide an intensive activity program for a group of young adult retardates in the trainable age but too old to participate in special classes. Thus, flexible use of funds can permit gaps to be filled in such areas as the transition from the special education to full community adjustment. While there is an increasing amount of State grants-in-aid funds devoted to mental retardation, initiative on allocation of these funds rests with the States and the total amount spent in this area has not increased as rapidly as we would like.

Technical assistance projects

Seven technical assistance projects in five States, directly on the subject of mental retardation, took place in 1961. This is more than all the previous technical assistance projects of the past 3 years on this subject. Pennsylvania covered several areas, including, Research Opportunities, Volunteer Services, Sheltered Workshops. Reviews of total State's needs, resources, and community problems and subsequent cooperative planning highlighted efforts in North Carolina, Mississippi, Tennessee, and Maine. These meetings, drawing on the best available consultants from NIMH and throughout the Nation have proven especially fruitful in that they bring together a working group of 40 or 50 individuals in a State and community and have shown to be successful in giving impetus, direction, and creativity to efforts to which they address themselves.

Consultation through regional offices

The Institute maintains a consultant staff in eight of the Department of Health, Education, and Welfare regional offices throughout the country. The consultants provide professional and technical assistance to a wide variety of programs in all of the States. The consultant staffs have become more active and have received more requests for consultation and assistance related to programs for the mentally retarded both in the community and the institutions. The recent increase in technical assistance projects in this field is but one example of this. The offices provide not only direct consultation on the basis of their own wide experience but draw upon expert resources from the Institute and from other consultants who can be retained by the Institute.

PERSONNEL

Training grants

For many years the Institute has been supporting professional trainings of persons in the basic mental health disciplines. The Institute has been involved in support of the training of over 10,000 professionals, psychiatrists, psychologists, social workers, nurses, social scientists, and others. Many of these devote part of their time to work in mental retardation and those involved in research have made significant contributions to the field.

Current support for psychiatry training has, as its locus, both State institutions, Letchworth Village, New York, and Walter E. Fernald School, Massachusetts, as well as the University of California where residents spend some time training in mental retardation.

Other support is for training grants in social work and psychology. Of note is the program at the George Peabody College for Teachers for the training of psychologists at the doctoral level with special competence in mental retardation. This program has developed over a dozen graduates since its inception in 1954, many of whom are in key positions in the field such as the current research director of the President's Panel on Mental Retardation.

Project support for training and staff development

Other mechanisms for the development of professional competence of personnel in the field is done through the Mental Health Projects Grant. The Western Interstate Commission for Higher Education in Colorado has begun an "Interstate Cooperation for Hosiptal Staff Development" program. This is a 3-year demonstration program of staff development in mental hospitals and schools for the retarded through interstate cooperation. The elements of the demonstration program are (*a*) regional conferences, (*b*) travel for career employees to observe and participate in selected new institution programs in other States, (*c*) continuation education programs to bring faculty to institutions, singularly or in groups, which are isolated from university centers. Working through the Western Mental Health Council, State mental administrators, and the regional offices of the U.S. Public Health Service, the program is demonstrating that the cooperative use of facilities on a regional basis can result in increased professional interaction between public facilities and training centers, and more efficient and effective use of personnel in public mental institutions.

The Southern Regional Education Board has begun a 3-year program entitled "A Regional Project to Improve Inservice Training of Attendant Personnel in Institutions for the Mentally Retarded." Purpose of this project is to improve the care of mentally retarded by developing and vigorously applying knowledge about living arrangements conducive to the growth, development, and welfare of the residents of State institutions. Strengthening and expanding the program of inservice training for attendant personnel are viewed as the most direct way to attack this problem. Key officials of 23 institutions have joined with the SREB to conduct a 5-year study action program to collect and develop information about such child care and to devise, adopt and test ways of applying this to the operation of the facility.

The central mechanism is a series of seminars attended by representatives of the participating institutions, staff of the project, and consultant personnel. A 3-day seminar, held in December 1961, brought together most of the superintendents of the State schools throughout the South and was considered highly successful in clarifying basic issues which will facilitate the full development of this most important program.

SUMMARY

The estimated expenditure of approximately $5 million for mental retardation by the Institute, estimated for 1962, is equal to the amounts spent by the Institute throughout the whole period of 1948 to 1960. This remarkable growth in funds has been paralleled by a heartening development of the field of mental retardation. The Institute has served to both initiate and support activities in areas of research, service, and personnel. The nature of the problem of mental retardation has led to cooperation with other organizations of the Public Health Service, including the National Institute of Neurological Diseases and Blindness, as well as the education, welfare, and vocational activities of the Department of Health, Education, and Welfare. At a crucial point in the development of this field, it has been highlighted by the President as a problem of national significance. The Institute will continue to work in a dedicated manner in the field of mental retardation.

ST. ELIZABETHS HOSPITAL RESEARCH CENTER

Mr. Fogarty. What about your project at St. Elizabeths?

Dr. Felix. This is continuing quite satisfactorily. As you know, we have assigned to us one building, the William A. White Building there. The director of the project, Dr. Elkes, also has a dual appointment now. Although he is on our payroll, he is assigned as Director of Research for the St. Elizabeths Hospital.

The Director of Clinical Research under him, Dr. Fritz Freyman is also Associate Director of Research for the hospital. They are doing studies there on large groups of patients where we were not able to do it at the Clinical Center because of the more restricted capacity and the types of studies we could do.

They have also now moved into two new activities. They are now working through an outpatient clinic which has been set up to follow the patients that they have seen in the hospital. They are taking residents from the rest of the hospital who rotate through this service and learn something about research and something about these newer methods of treatment and care.

They are also taking nurses in rotation so that they are orienting a lot of other people in this type of activity.

STUDY OF BEHAVIORAL SCIENCES

St. Elizabeths Hospital on their own has set up, as a result of this stimulation, a center for the study of behavioral sciences under one of their own staff, which is in their own budget, and which is in a building next door to the William A. White Building—which was formerly the TB pavilion.

They have taken the top floor of that building and converted it into a series of laboratories and hospital rooms for study in the behavioral sciences of these patients.

As a result of our work over there, they have developed, and it has been widely disseminated and widely accepted, an improved design for the so-called double blind study and evaluation of psychoactive drugs.

It is a much more effective way of doing it. They draw in ward personnel by having them fill out certain types of questionnaires which is within their capacity to do. This is attracting a great deal of attention, not only here but over the world.

I don't want to call it a problem, but one of the things with which we have to deal is the large number of people from this country and abroad who come and visit. I suspect that a quarter of Dr. Elkes' and Dr. Freyman's time is taken up with really important, distinguished people from over the United States and abroad who want to come and spend a few hours to a few days. We feel this is important, and it is a part of his assigned duties. But it does take his time.

RESEARCH RESULTS

Mr. Fogarty. What are some of the results now?

Dr. Felix. It hasn't been going long enough yet for us to have any conclusive results in terms of their actual research projects. The results have been of another nature.

It has had an effect upon the entire St. Elizabeths Hospital from the point of view of the type of staffing and care of patients on the wards of the hospital, which has meant a shortened stay where they have been able to institute it.

As far as the scientific results are concerned, they have only been in existence 2 or 3 years, and these are long-term studies they are carrying on on animals and humans.

Mr. Fogarty. You are satisfied with their progress?

Dr. Felix. I am delighted.

LEXINGTON DRUG ADDICTION RESEARCH CENTER

Mr. Fogarty. What are you doing in Lexington?

Dr. Felix. In Lexington, we are studying, as you know—there are two or three different kinds of studies going on there. One is the evaluation at the clinical level of new synthetic narcotic drugs to test them for clinical efficiency, for pain-relieving qualities, and some other effects of this nature.

Out of this has come a new drug which I described here last year which is as effective as codeine in relieving cough and pain, and is essentially nonaddicting. They have also been able to develop and test a new constipating drug which is nonaddicting. This is something for which they have used opium since time immemorial, paregoric, things of that nature, where they have need for constipating. They have developed this.

They have not yet developed an actual pain reliever which is as effective in relieving pain as morphine and is less addicting, although they are moving in this direction. They are testing now some phenothiazine drugs. That is, the same group of substances from which come chlorpromazine and some of these other tranquilizers.

Mr. Fogarty. Wasn't there a very effective new painkiller developed a couple of years ago?

Dr. Felix. That was developed by the Arthritis Institute and has been tested by them. I can supply that for the record. I don't have it completely—or prehaps Dr. Daft had better speak to it when he comes up because he knows much more about it. That is in distribution, yes, sir.

They are also doing fundamental studies on the effect of drugs of various kinds, barbiturates and tranquilizing drugs on animals as a preliminary step to the development of more effective types of tranquilizing drugs and barbiturates.

DECLINE IN NUMBER OF DRUG ADDICTS

Mr. Fogarty. On the problem of narcotics here is an article saying that H. J. Anslinger, U.S. Commissioner of Narcotics, reports that the number of known new narcotic addicts in 1960 was 7,479, which is 1,858 fewer than the number for 1956.

The percentage of addicts under 21 years of age dropped from 12 in 1956 to 3.9 in 1960. Is that so? I have been hearing Members of Congress asking questions about this. In the larger cities they claim it is going up, especially in the teenage group. I am talking about New York City now, for one.

Dr. FELIX. I don't know those data. Those are the Commissioner's. But I suspect they are for the United States as a whole. I may be quite wrong.

Mr. FOGARTY. This article says:

> Anslinger advocates the building of community facilities, similar to the Federal hospitals at Lexington, Ky., and Fort Worth Tex., for treatment and rehabilitation of addicts. A new hospital of this kind is under construction in New Jersey.

This is a Public Health Service Report of August 1961.

What is this hospital in New Jersey? Is it a private hospital? Is it being built with the help of Government funds, or what? Do you know?

Dr. FELIX. I will supply that.

Mr. FOGARTY. You can also supply where it is located.

(The requested information follows:)

> There is legislation pending in Congress (H.R. 5999, introduced Mar. 28, 1961, by Mr. Daniels of New Jersey) which would authorize the construction of a hospital by the Federal Government in the State of New Jersey for persons addicted to drugs. This hospital would be similar in characteristics to those currently operated by the Bureau of Medical Services of the Public Health Service at Lexington, Ky., and Forth Worth, Tex., except that the bill also would authorize the Surgeon General to enter into agreements with the State of New Jersey and neighboring States for the joint operation of the hospital.

STUDIES ON ADDICTION

Dr. FELIX. There have been a number of studies in New York City, in Illinois, in California. There are some very interesting developments in each of these.

California in 1961 enacted some legislation pertaining to addiction which requires the registration by the local law enforcement authorities of persons convicted of or released from confinement for narcotic addiction, and for the involuntary commitment of narcotic addicts. They also have developed halfway houses there for rehabilitation of the addict.

In Chicago, in August of 1960, they developed a narcotic withdrawal ward at the Bridewell Hospital, which is associated with the city of Chicago.

SPECIAL REPORT ON DRUG ADDICTION

Mr. FOGARTY. We will place your special report in the record.

(The report follows:)

INTRODUCTION

The National Institute of Mental Health is continuing to make a broad and diversified attack on the problem of drug addiction. This ranges from studies pertaining to the biochemical effects of narcotic drugs to encouragement of program development in local areas so their health and social agencies will provide services to drug addicts and their families as necessary. The major work on drug addiction in the National Institute of Mental Health is being carried on through the functions of the community mental health services, by intramural research conducted by Institute staff and by research grants.

OVERVIEW

Although there are many unknowns concerning the development of drug addiction, progress is being made in its understanding. Drug addiction is a complex problem which probably results from many factors both within the person and in his social environment. Further knowledge of the life history of the addicts, of the impact of social and environmental factors upon them, and evaluative studies of different treatment methods are especially needed.

The great interest of a few years ago in the tranquilizing and psychotomimetic drugs has had a stimulating effect on research on narcotic drugs. More attention than formerly is given to the basic mechanisms of drug action. Narcotic drugs are often included in investigations focused on the new psychopharmacological drugs.

In the area of treatment, care, and rehabilitation of drug addicts, it will probably be necessary to consider drug addiction as a chronic, often intermittent type of illness, like some other forms of psychiatric disorder. It is becoming increasingly clear that hospital care alone is insufficient and that followup, rehabilitative services in the community are essential in the posthospital phase.

CONSULTATION, TECHNICAL ASSISTANCE, AND DEMONSTRATIONS

During the year, the Institute provided technical assistance and consultation in several States based on expressed interest in coping more fully with the problem of drug addiction.

In 1957, the U.S. Public Health Service Demonstration Center, in New York City, was established by the Community Services Branch, National Institute of Mental Health, as a pilot project by which selected patients, returning to that city after discharge from the Public Health Service Hospital in Lexington, Ky., would be referred to appropriate community agencies. The goals of the project were: (1) To assist these agencies to extend their services to drug addicts, and (2) to continue a longitudinal study of the patterns of relapse and adjustment to the community found in a sample of the dischargees from the hospital. An advisory committee was appointed to the center. Its members represented a number of city and State health and welfare agencies concerned with problems of drug addiction. Staff of the center worked in various ways to establish satisfactory relations with community agencies. Its staff offered consultative services to agencies and more of them began to give attention to the drug addict. The presence on the advisory committee of personnel from the various agencies and consultation to them from the demonstration center has, we believe, contributed a great deal to further development of programs in the area of narcotic addiction. During the past 2 years, the New York City Department of Health and the New York Community Mental Health Board showed increasing interest in assuming some responsibility relative to narcotic addiction. Currently, the demonstration center staff is writing up the report on its activities. The functions of the center as a pilot project are being gradually terminated. In order to profit as fully as possible from the experience of the social work staff of the center and the interest of the two local agencies mentioned above, a new proposal is being developed which will function within the framework of a local health department (district).

Through contractual arrangement, the National Institute of Mental Health will work with the New York City Department of Health and the New York Community Mental Health Board in carrying out the new project, which will include services by social workers and public health nurses, for work with narcotic addicts and their families.

STATE AND LOCAL PROGRAMS

As part of a treatment and research program for narcotic prisoners at the California Institution for Men at Chino, near Los Angeles, a parole system has been established for addicts in which a condition of parole may be participation in the experimental program. In this program, parole agents carry a caseload of 30 former prisoners. In addition to individual counseling, each parole agent does group counseling, mostly in the evening hours. The project is also testing the effectiveness of drugs like Nalline in the detection, control, and treatment of addiction. If an addict is found to be taking narcotics, he may be returned to prison. The original appropriation for this project was $125,000 in 1958. In 1960, the California Legislature raised the appropriation to $500,000, which made possible the opening of similar service units in other parts of the State.

In 1961, the California Legislature enacted legislation pertaining to narcotic addiction. It requires registration with local law enforcement authorities of persons convicted of, or released from confinement for, certain specified narcotics offenses, after effective date of act. In addition, procedures are provided for the involuntary commitment of a narcotic addict or person in imminent danger of narcotic addiction to custody of the director of corrections. The same bill establishes an institution in department of corrections for narcotic addicts and persons in imminent danger of narcotic addiction. It authorizes transfer of youth authority wards to such institution.

Another bill "specifies that section, which lists places in which persons can be treated for narcotic addiction, and other provisions of division relating to narcotics, do not prohibit maintenance of a place in which persons seeking to recover from narcotics addiction reside and endeavor to aid one another and receive aid from others in recovery from such addiction, and that such provisions do not prohibit such aid, provided that no person is treated for addiction in such place by means of administering, furnishing or prescribing of narcotics." The enactment of this law should make it easier for "halfway houses" to be established for narcotic addicts.

In June 1961, the Attorney General and Director, California Department of Justice, submitted a 15-page "Report on the Synthetic Opiate Antinarcotic Testing Program" to the California Legislature. It includes information on "antinarcotic testing clinics" established in a few counties of California and comments upon the "nalorphine test" which is used in those clinics. The report points out that the pupillary test with synthetic opiate antinarcotics is a useful tool for determining whether an individual is a narcotics user, but that a single test involving the change in pupil size alone is insufficient evidence to establish this fact beyond a reasonable doubt.

In August 1960 a narcotic withdrawal ward was established at Bridewell Hospital (associated with the city of Chicago, Ill., jail system). During the first 4 months, 101 patients had been admitted for care. The majority were referred by court order although a few patients voluntarily committed themselves for withdrawal care. There also have been a few cases transferred from the general wards of the Bridewell Hospital to the narcotic ward.

At Institute for Alcoholism and Narcotic Addiction was established in Philadelphia, Pa. In early January 1961, some of its staff went to the Public Health Service hospital in Lexington for an orientation period. The institute is a part of the division of behavioral problems, State department of health, and has a collaborative relationship with the Philadelphia Department of Health and Philadelphia General Hospital. Financial support is a combination of State and city funds.

The Narcotic Control Commission of New Jersey continues to be active. It publishes an informative annual report and has interest in encouraging the development of treatment services within the State.

Since 1959, New York has taken several major steps to strengthen its program for narcotic addiction. A State appropriation of $300,000 made it possible to open a research facility at Manhattan State Hospital. Its 55-bed unit is the basic one for research on narcotic addiction.

More recently, the New York State Department of Mental Hygiene has established two new units for the care, treatment, and rehabilitation of narcotic addicts. An 80-bed inpatient unit to serve the downstate area was opened in April 1961 at Central Islip State Hospital, Long Island, while the other, a 20-bed inpatient unit, is located at Utica State Hospital to serve patients in the upstate area. In January 1959, New York City's Department of Hospitals accepted responsibility for narcotic addicts who committed themselves voluntarily. That department may refer the patient to a mental health clinic in a city hospital or may provide inpatient care. Riverside Hospital, which is also part of New York City's Department of Hospitals, continues to provide inpatient and outpatient care for drug addicts under 21 years of age. The New York State Health Department, State mental hygiene department, and the New York City Community Mental Health Board contribute to the support of the program at Riverside Hospital. At that hospital, approximately 15 percent of 2,280 first admissions in the initial 8½-year period were self-referrals. Five of the 2,280 first admissions were 13 years of age and 175 were over 21. The 18-, 19-, and 20-year age groups accounted for 1,478 of the 2,280.

The New York State Division of Parole issued a report evaluating their 3-year "Special Narcotics Projects" which began in 1956. In this experimental project, four well-trained caseworkers tested the efficacy of intensive "authoritative" casework with a small group of young drug addicts on parole. In the last year of the demonstration, group therapy sessions were conducted by a psychologist. Although the evidence was not conclusive, there were many indications of the success of the service and the Governor has recommended that the project become a permanent part of the operations of the division of parole.

Within New York City, there has been increased evidence of interest in the problem of narcotic addiction. For example, the assistant commissioner, New York City Department of Health, was designated in early 1961 by the mayor as "New York City Coordinator for Adolescent Narcotic Addiction Activities." For several months, the Community Council of New York City had a "Subcommittee on Survey of Community Resources for Narcotic Addiction." It completed and assembled a nonevaluative summary of those resources which were available in New York City. The assistant commissioner has recommended that the city department of health establish a division for addictive disorders. The proposed division would have functions relative to alcoholism as well as narcotic addiction. Several of the community resources for narcotic addicts are agencies to which personnel of the demonstration center made referrals, provided consultation, and in other ways secured their involvement in program development.

INTRAMURAL RESEARCH

Tests of new drugs

Testing the addiction liabilities of new narcotic drugs remains an important part of the research program of the Institute at the Addiction Research Center, U.S. Public Health Service Hospital, Lexington, Ky. This work is closely coordinated with the program of the Committee on Drug Addiction and Narcotics, National Research Council. The studies have four purposes:

(1) To provide information on the degree of addictiveness of newly discovered agents that are likely to come into the market. This information is necessary to determine whether these drugs should be subjected to national or international legal control.

(2) To develop pain-relieving, cough-suppressing and constipating drugs with reduced addictiveness.

(3) To provide information on therapeutic and toxic properties of these drugs before they are introduced into clinical practices.

(4) To elucidate the basic mechanisms and tolerance, habituation, physical dependence and other aspects of drug addiction.

Following many years of discouraging results, it now appears possible to develop drugs with reduced addictive liabilities. The program has developed materials for the relief of cough which are not addictive (dextromethorphan, narcotine), an effective constipating agent with minimal addictiveness (diphenoxylate of R–1132), and two drugs that are as effective as codeine for the relief of pain but with reduced addictiveness (dextro-proproxphene and the isoquinoline compound known as I–K–1). There is as yet however no drug that is as effective as and less addictive than morphine for pain relief, but investigations are proceeding with a member of the phenothiazine group (levomepromazine) that has been reported to be as effective as morphine for relief of postoperative pain, and with a new series (the indanes) which, though analgesic, have spectrums of pharmacological effects quite different from those of morphine.

Neurophysiological studies

Neurophysiological studies at the Addiction Research Center have been following two main lines: (1) Investigation of the changes occurring during addiction to opiates in experimental animals, and (2) investigation of changes occurring during cycles of barbiturate addiction in cats or dogs. Studies on opiate addiction have been facilitated by the development of a technique for developing tolerance and physical dependence in dogs within a few hours by the continuous infusion of morphine. This method is already being used as an additional procedure for evaluating the addictiveness of new drugs in animals. However, physiological differences of a quantitative nature between acute and chronic physical dependence have been found. Changes in acute tolerance and dependence are mediated by mechanisms above the level of the spinal cord, whereas the changes in chronic dependence are mediated by mechanisms at the spinal as well as at supraspinal levels. The work has led to the development of an hypothesis that the basic physiological change in tolerance and dependence may consist of an increase in the activity of nervous pathways that are parallel to normal nervous pathways, but which become operative only when the primary pathways are depressed by morphine. Efforts to test this hypothesis are underway.

Studies on the neurophysiology of barbiturate addiction currently consist of: (1) Attempts to localize the sites within the nervous system responsible for the syndrome of abstinence from barbiturates, and (2) studies on possible changes in neuro-humoral mechanisms during addiction to barbiturates. It has already been shown that the cerebral cortex plays a major role in the development of addiction to barbiturates, since decorticated dogs are more resistant to the effects of barbiturates and have fewer withdrawal seizures. The role of the cerebellum is now being investigated and eventually the studies will include changes in brainstem centers. A mixture of the amino acids, *l*-arginine and glutamic acid, partly suppressed withdrawal seizures in some addicted dogs. Since administration of these amino acids may raise the level of gamma amino butyric acid in brain it is possible that changes in the brain level of GABA are correlated with the development of addiction to barbiturates.

Biochemical studies

Biochemical studies have been concerned with the levels of the neurohumors, epinephrine and norepinephrine, in brain and other organs during cycles of addiction in rats. Morphine induces only slight changes in the levels of these materials when given in single dose or even when given chronically. Following withdrawal of morphine, levels of catecholamines in the adrenal gland are markedly elevated. The studies are continuing. Sensitive and specific methods for detecting opiates and meperidine in urine have been developed and are in use.

Psychological studies

The Addiction Research Center Inventory for assessing the subjective effects induced by various drugs was further refined during the year. The inventory developed by the psychological staff distinguishes between the various types of drugs of interest to the Addiction Research Center and gives good dose-response curves. Subscales of the main inventory are now being used in clinical studies on opiates and psychotomimetic drugs.

Additional data on the relationship of social deviance to addiction was obtained during the year, and a general hypothesis of the etiology of addiction in the United States emphasizing the importance of social deviance has been developed. Future studies will be framed in terms of the main hypothesis. Collection of data on judgment of odds by psychopaths and nonpsychopaths is being continued, and have confirmed the original finding that the behavior of psychopaths is more influenced by the objective odds of chance occurrences than is the behavior of normal persons.

Using rats, the psychological section has been able to show that only morphine and similar drugs give significant dose-response curves in reducing pain-conditioned anxiety in rats. Attempts to develop experimental analogs of relapse in humans are being continued. It has been shown that rats become addicted to the potent morphinelike drug, I–G–2, and that as addiction proceeds the rats lose their initial aversion to solutions of this substance. As yet however they have not succeeded in inducing relapse in formerly addicted rats, but these studies are continuing and may be extended to monkeys in collaboration with the University of Michigan.

Psychotomimetic drugs

The studies on psychotomimetic drugs are carried out because cocaine, marihuana, and mescaline (the active principle in the peyote cactus used by American Indians) induce temporary psychotic states in man and are important problems in public health in the United States and in other parts of the world. In addition, investigation of these agents is important to research on schizophrenia and other natural psychoses. Previously it was shown that administration of increasing daily doses of LSD–25, psilocybin, or mescaline results in diminishing effects (tolerance). Patients who were tolerant to any of these drugs were also tolerant to the other two. However, patients made tolerant to amphetamine were not also tolerant to LSD, indicating that mescaline, psilocybin and LSD do not induce toxic psychoses by an "adrenergic" or epinephrinelike action. The studies are now being extended to the cholinergic blocking drugs (scopolamine, atropine) and the piperidyl benzylates.

EXTRAMURAL RESEARCH

Research grants awarded through the Research Grants and Fellowships Branch and the Psychopharmacology Service Center include a large number relating to drug addiction.

Six grants totaling $85,289 have been categorized in one category alone, namely, drug addiction. Fifteen additional grants, for a total of $360,670, relate to drug addiction, but have been categorized in more than one area. The research supported by those grants represents a broad attack on the problem, including, for example, studies of biochemical and metabolic effects of addiction; tests of new drugs designed to block the addictive properties of morphine-type drugs, while permitting their desirable, analgesic effects to go on unhindered; long-term assessments of the posthospital adjustment of addicts; and analyses of personality characteristics among those prone to addiction.

Several months ago, the National Institute of Mental Health was approached by a group from Illinois, representing the State of Illinois narcotic control division, as to the possibility of developing a simple, rapid urine test for the presence of opium alkaloids. The division has responsibility for following all identified drug addicts after these individuals have completed prison sentences or periods of hospitalization. At present these postaddicts are being followed by a Nalline test and equally cumbersome and expensive urinary determinations.

Based in part on the interest of the Illinois personnel, a group of 11 experts in drug addiction and opiate chemistry met at Bethesda on December 16, 1960. The meeting was also attended by scientists connected with narcotic addiction programs in Illinois, California, and New York, the three States with the largest drug addiction problem.

The meeting began by discussing the adequacy of the Nalline test as it is now used in both California and Illinois. It was agreed that the Nalline test, particularly when pupillary change is the only measure of Nalline effect utilized, is relatively unreliable. Data from both Illinois and California showed that modest numbers of individuals with positive Nalline tests failed to show opiates in their urine and modest numbers of individuals with negative Nalline tests did show opiates in the urine. The group agreed that work on the development of better and more efficient methods for the routine analysis of urines for opiate alkaloids was highly desirable because of the growing volume of work of this sort in States such as California and Illinois which were closely following identified drug addicts to detect recidivism at an early stage. The further work needed to establish the practicability of utilizing gas chromatographs for the routine analysis of urine samples was felt by the group to deserve a high priority.

At this time, a research project pertaining to development of a rapid test for narcotic excretion is being carried on in the Department of Pharmacology and Toxicology, University of Wisconsin. The specific aim of the proposed work is to develop a rapid and accurate procedure for the detection of opiate alkaloids in urine. It is also proposed to apply the techniques developed during the study to problems relating to the excretion of opiates. A simplified, rapid, yet thoroughly reliable method for the identification or exclusion of narcotic drugs in urine could do much not only in the primary detection of addicts, but also it would be helpful in deterring the abstinent addict from relapse, knowing as he would that his detection would be prompt and certain if using narcotics.

TRAINING AND EDUCATION

The general graduate training in the mental health professions, which receive support through the Institute, includes preparation for a number of specialties. Within this preparation, training toward competence for working in the area of drug addiction might well be included.

For many years, the Public Health Service hospitals in Fort Worth and Lexington and the Institute Addiction Research Center have provided training for personnel from the United States and many foreign countries. This training in clinical care and research has been for psychiatrists and other medical personnel, nurses, psychiatric aides, psychologists, chaplains, and students of medicine and pharmacy. Staffs from the two hospitals and the Center have participated in many professional meetings and are the authors of significant publications.

It is of importance also to note that the two hospitals and the Center have been visited for various lengths of time by personnel from many States and foreign countries as an aid to them in program development at their respective locations.

PROFESSIONAL ASSOCIATIONS

The 1959 Conference of the Surgeon General with State and territorial mental health authorities adopted a recommendation encouraging the Public Health Service to establish an ad hoc committee of State mental health and Hill-Burton authorities to work with it in formulating treatment and administrative guidelines which State agencies could use in developing a statewide plan for mental health facilities. The ad hoc committee was appointed in 1959 and its report, Planning of Facilities for Mental Health Services, was published in 1961 as Public Health Service Publication No. 808. Drug addiction was one of a few social problem areas which received attention by that ad hoc committee and is mentioned in the report.

The work of the joint committee of the American Bar Association and the American Medical Association on narcotic drugs marked an important cooperative undertaking between two important professions. The interim and final reports of that joint committee were made available to the general public in 1961 by an Indiana University Press publication, Drug Addiction: Crime or Disease.

The American Bar Foundation, as a legal research organization, neared completion of its study, Narcotics and Law, in the field of narcotic drug laws.

FISCAL OBLIGATIONS

Below is a summary of NIMH obligations in the field of drug addiction for the fiscal years 1959–63:

Fiscal year—Year	*Research grants*	*Training grants*	*Direct obligations*	*Total obligations*
1959	$363, 846	----------	$266, 358	$630, 204
1960	433, 302	----------	335, 113	768, 415
1961	445, 959	----------	354, 626	800, 585
1962	810, 000	----------	454, 000	1, 264, 000
1963	950, 000	----------	454, 000	1, 404, 000
Total	3, 003, 107	----------	1, 864, 097	4, 867, 204

TRANQUILIZERS

Mr. **Fogarty.** Has a problem in tranquilizers developed, Dr. Felix? They tell me the vitamin business is going down and the tranquilizing business is going up. A few years ago vitamins were the thing. Everybody was taking them for everything under the sun.

Are problems developing along with the increased use of tranquilizers?

Dr. **Felix.** I do not believe, Mr. Chairman, that a tranquilizer can be purchased over the counter in any State. I think it can be obtained only on prescription.

As far as I know, there is no State—I may be wrong and I will check to be sure—but I believe there is no State in which a person can go and buy tranquilizers over the counter as they would aspirin.

Mr. **Fogarty.** What about barbiturates?

Dr. **Felix.** They are by prescription, too; yes, sir.

Mr. **Fogarty.** What about some of these things you see advertised which are supposed to do about the same thing?

Dr. **Felix.** They don't contain barbiturates. They are antihistamines or some other substance of this nature which have a tranquilizing-like effect; but they are not tranquilizers. They don't affect the central nervous system in the same way.

Mr. FOGARTY. They have about the same effect as if you took a couple of aspirins. Is it because many of these things that you see advertised in the newspapers and on television lead people to think they are, in effect, tranquilizers? Maybe that contributes to the figures I have seen.

Dr. FELIX. This may be. I am sure that these companies— reputable companies—would not intentionally mislead people. But people may get this impression from the advertising inadvertently.

Mr. FOGARTY. We have a Federal Trade Commission. If they were all honest, we wouldn't have a Federal Trade Commission, would we?

Dr. FELIX. Or, because we have a Federal Trade Commission, they are all honest—one of the two.

Mr. FOGARTY. Are there any problems in the use of tranquilizers that you know of which need attention?

Dr. FELIX. Nothing that has come to my attention of a serious nature. There has been misuse of tranquilizers. In some cases they are being used for conditions in which other substances would have done better. But these are isolated instances.

I have felt that this was one substance, since it went under control so that it can only be dispensed by prescription, and as there has been increasing information given to physicians, which has probably been developing more soundly and intelligently than any substance I know of.

PSYCHOPHARMACOLOGY SERVICE CENTER

You know, we have in the Psychopharmacology Service Center this information service which will be combined with our clearinghouse once we get it set up.

Mr. FOGARTY. How is this Psychopharmacology Center doing?

Dr. FELIX. Very well.

Mr. FOGARTY. We urged you a few years ago to get going, remember.

Dr. FELIX. That is correct; you did. We now supply information on the newer drugs as they are tested and come in in reports from the grantees and other sources. I think it is something in the neighborhood of 4,200 subscribers who are on the mailing list. They request this, and we put them on our mailing list.

This will have to expand more as time goes on, but we have now in our files something over 17,000 articles about the various drugs—abstracts of them. We have this on punchcards so that they can be sorted and get the records on a lot of different criteria.

SPECIAL REPORT PSYCHOPHARMACOLOGY SERVICE CENTER PROGRAM

Mr. FOGARTY. We will put in the special report in the record at this point.

(The report follows:)

INTRODUCTION

During the past year the psychopharmacology program of the National Institute of Mental Health has made substantial progress with special clinical drug evaluation research programs initiated during the preceding year. Important new research developments have also emerged from both the basic and clinical research projects under grant support. In addition, expanded services in the areas of data analysis and scientific information have been made available to investigators in psychopharmacology.

CURRENT CLINICAL RESEARCH

New drug developments

The past year has not been noteworthy for the emergence of new types of drugs that affect behavior. Work by many investigators has involved such new phenothiazine derivatives as carphenazine and thioperazine, and thioxanthene derivatives, such as chlorprothixene—drugs closely related to the phenothiazines—with no finding of truly unusual new properties. The two phenothiazine derivatives, however, are reported to be quite effective in the treatment of acute and chronic schizophrenic states. A grant-supported investigator at Baylor University, with extensive experience with these compounds and other closely related antidepressives, imipramine and amitriptyline, has suggested that there is a spectrum of clinical efficacy running from strong antipsychotic potency in several phenothiazine derivatives through to strong antidepressive activity in the imipraminelike drugs, with compounds intermediate in chemical structure such as the thioxanthenes possessing varying degrees of both properties.

An interesting tranquilizing drug of totally different chemical structure, haloperidol, has been reported by European investigators as effective in the treatment of acute schizophrenic states, and producing neurological side effects similar to those observed with the phenothiazines. In preliminary studies American investigators, including several grantees, have reported this drug to be relatively ineffective. A definitive controlled study comparing this drug with a potent phenothiazine, thiopropazate, has been completed under an early clinical drug evaluation grant to Stanford University supporting collaborative work in several Veterans' Administration hospitals. The data are now under analysis.

Chlordiazepoxide deserves mention as an outstanding member of a group of tranquilizing drugs which do not appear to possess phenothiazinelike efficacy in psychotic states, but which are claimed to be effective in the treatment of anxiety associated with other psychiatric conditions. Two recent controlled studies reported in a British journal, the Journal of Mental Science, have shown it to be strikingly more effective than placebo in anxious neurotic patients, findings confirming preliminary studies in the American literature. A grantee at Stanford University has reported that this drug is capable of producing physiological withdrawal symptoms similar to those encountered with meprobamate and the barbiturates when these are administered in high dosages for prolonged periods and then abruptly withdrawn. It may be that most of the compounds used in the treatment of neurotic anxiety which possess some sedative action could also be shown to produce withdrawal reactions of this type if administered in a similar manner. Fortunately, this high-dosage therapy followed by abrupt stopping of medication is not employed in usual clinical practice. Grantees at the University of Pennsylvania, the New York State Psychiatric Institute and New York University are currently carrying out controlled studies of chlordiazepoxide and the results of this work should be available in the coming year. Several other grant-supported units are studying diazepam, a new analog of chlordiazepoxide.

The major development in the field of antidepressive medication has been the identification by several groups, including Dr. Bernard Brodie's laboratory at the National Heart Institute, of demethylated metabolites of imipramine and amitriptyline. These naturally occurring metabolites of drugs in current clinical use have been reported to be at least as effective as their parent compounds and to act more rapidly in the control of depressive symptoms. It is entirely possible that the clinical effectiveness of imipramine and amitriptyline, drugs which ordinarily do not produce symptom alleviation for from 7 to 20 days, may be due to the conversion of these compounds by the body to the monodemethylated form. A controlled study of desmethylimipramine in depressive states is now being carried out at eight Veterans' Administration hospitals under grant support through Stanford University as a part of the Psychopharmacology Service Center's early clinical drug evaluation program.

Early clinical drug evaluation program

In the late fall of 1960 a program of special grant support was developed by the National Institute of Mental Health in recognition of need for early clinical drug evaluation. This program is intended to support trials of promising agents to determine their safety, appropriate dose ranges, and side effects as well as to collect preliminary evidence of clinical effectiveness in particular symptoms or syndromes. A total of 26 grant applications was received in response to the announcement of this special program. Eleven of these were approved as being most appropriate for support under this program. Nine of the grants went into effect in July 1961; two of the grantees from outside of the United States received their awards in late 1961 and consequently, their programs did not begin until later in the year. Four early clinical drug evaluation units had already been supported by the National Institute of Mental Health under the regular grant program before the instigation of the special program, bringing the total to 15.

As is appropriate in terms of the current public health used, the program at present gives major emphasis to the evalution of drugs useful for acute and chronic schizophrenics; and provides more limited facilities for the evaluation of drugs in depressive patients, neurotic outpatients, alcoholics, and other special psychiatric diagnostic groups. One unit at New York University is focusing upon the evaluation, in children with psychiatric disorders, of drugs already shown to be safe and effective in adult patients. Since psychiatric disorders of childhood react differently to many drugs (for example, hyperkinetic overactive children are tranquilized by amphetamine), special studies in this particular group are clearly necessary.

During the coming year it should be possible to expand the number of early clinical drug evaluation units, with emphasis on the development of units capable of giving special attention to the psychiatric diagnosis categories currently less well covered.

The 13 units fully underway as of December 1961 were studying approximately 45 new psychotropic compounds, the major of which are experimental. Seven units are engaged in very early testing of these drugs. The other six units are concentrating on smaller controlled comparative studies at a somewhat later phase in the early clinical drug evaluation.

Since the program went into effect, the principal investigators of the existing units have met with the staff of the Psychopharmacology Service Center on two occasions, and active contact with the units has been maintained through frequent site visits.

CLINICAL STUDIES OF PHENOTHIAZINE DERIVATIVES

Impact of phenothiazines on psychiatric care

There is continuing evidence that drug treatments for hospitalized schizophrenic patients are having a significant impact upon mental hospital populations. Dr. Henry Brill, deputy commissioner of the New York State Department of Mental Hygiene, has recently reported a continuing decrease in the number of hospitalized schizophrenic patients in the New York State hospital system over the past 5 years, in the face of an increased number of new admissions each year. In addition, he has found that the number of schizophrenic patients continuously hospitalized for 5 years following admission—the hard core of treatment-resistant patients—has dropped approximately 20 percent over the past 5 years. Although other significant changes have occurred in the New York State hospital system during this period, Dr. Brill feels that drug treatment has been a major factor in this dramatic reversal since 1956 of the earlier trend marked by a steady increase in number of patients hospitalized every year.

A grant-supported study by investigators in the California Department of Mental Hygiene of release rates of male scizophrenic patients has produced a report which raises interesting questions concerning the mechanism by which this decrease has occurred. In the study of male schizophrenic patients who did and who did not receive drug treatment during their initial period of the hospitalization, no differences were observed in release rates between the drug-treated and non-drug-treated groups. These results confirm an earlier grant-supported study by an investigator at Catholic University who arrived at similar findings on a survey of release rates for drug and non-drug-treated patients hospitalized at St. Elizabeths Hospital in Washington, D.C. It may well be that drugs, through effectively controlling the symptoms of seriously ill schiophrenic patients, may also contribute to a general improvement of hospital milieu, leading to better response in schizophrenic patients not so seriously ill as to warrant drug treatment.

Further grant-supported work with chronic schizophrenic patients treated in outpatient clinics has continued to underline the utility of drugs in this type of patient. Work at Kings County Hospital in Brooklyn has not only shown that chlorpromazine is much more effective than inert placebo in preventing hospitalization, but that it also produced significantly greater improvement in the social adjustment of patients remaining in the community. A detailed 5-year follow-up of 160 released hospital patients has been reported by the Manhattan Aftercare Clinic. Twenty-nine of these patients had been on continuous drug treatment for the entire period, while most of the other patients were on drug treatment following release and again later to prevent incipient relapses. A quarter of the patients, almost all of whom were on drug treatment, have been gainfully employed without showing adverse drug effects on ability to learn or on job performance. Maintenance drug therapy has also apparently not interfered with normal pregnancies in 14 of these patients. The patient's failure to take the drugs was a major cause of rehospitalization in this cohort.

The report by the New York State Department of Mental Hygiene on the effects of 5-years' drug treatment on their population has also provided indirect evidence of the safety of chronic administration of ataractic drugs, since age-specific mortality rates for their populations have not changed over the past 5 years.

Collaborative study of phenothiazine derivatives

The first major collaborative drug evaluation project in this area to be developed by the Psychopharmacology Service Center is a nine-hospital collaborative study of three phenothiazines (chlorpromazine, thioridazine and fluphenazine). This study, begun last year, is entering its final data collection phase which should terminate in June of 1962. A preliminary analysis of the first third of the patients studied has provided strong evidence that all three drugs are highly effective in the treatment of newly admitted patients with acute schizophrenia in all three types of hospitals included in the study. (State mental hospitals, psychiatric services of city hospitals, and private or university-affiliated intensive treatment centers). The drugs have been found to alleviate not only excitement, motor overactivity and schizophrenic thought disorder, but also withdrawal and apathy. Although more detailed analyses of the full data from the study will undoubtedly yield further findings, it is of interest that no major differences in symptom reduction between the three types of hospitals or between the three drugs have emerged to date.

Complete analysis of the full data should provide definitive evidence on the following points: (1) Do these three pharmacologically quite different phenothiazine derivatives differ in effectiveness in reducing specific schizophrenic symptoms; (2) Do they differ significantly in the type and severity of their side effects; (3) Does the type of hospital setting or the type of patient admitted to any one of the nine hospitals significantly alter the general effectiveness of these drugs or their effectiveness on specific symptoms; (4) On the basis of psychiatric history factors or presenting symptoms, can patients doing well on one of the three drugs be differentiated from patients doing well on another drug, i.e., can specific differential indications for the use of each phenothiazine derivative be identified. Answers to these questions should be clearly established by the fall of 1962.

It should be noted that this first major collaborative study to be developed by the Psychopharmacology Service Center has been progressing smoothly and effectively, with considerable evidence that the clinical ratings being made in all nine hospitals are of a high order of sensitivity, with a correspondingly low "error term," the statistical measure of the amount of irrelevant variability in the measuring devices which, if large, would confuse and confound the results of the research.

An incidental finding of the study has been the small fraction (less than one-fourth) of schizophrenic admissions to the nine participating hospitals who meet the criteria for inclusion in this study. The remaining three-fourths were found to be too chronically ill or too old (over 45) to be included, or were eliminated because their schizophrenic illness was complicated by alcoholism, mental deficiency or possible organic brain damage. The young, uncomplicated, acute schizophrenic patient, often thought to be the typical schizophrenic patient treated on the admitting services of State hospitals or on the psychiatric wards of city hospitals, appears to constitute only a minority of the schizophrenic patients admitted to these facilities.

For this reason, a second collaborative study using a simplified protocol is being developed to determine whether findings in the first study dealing with this restricted subsample of newly admitted schizophrenic patients apply also to the larger total group of schizophrenic admissions. New information on additional drugs will also be sought.

Improved techniques for analysis of data should permit new information to be obtained from both this and from similar collaborative studies being carried out with the Veterans' Administration.

Other clinical studies of phenothiazines

The psychiatric drug literature continues to be conspicuously lacking in clinical hypotheses concerning differences between similar drugs or differences in the way clinical subgroups respond to the same drug.

A notable exception is a recent report from a grant-supported group at Hillside Hospital who have been carefully observing patients treated with chlorpromazine and have developed a series of specific behavioral typology of drug response. For example, they have found striking differences in the response of two groups of patients, both of whom would ordinarily be diagnosed as having paranoid schizophrenia. The first group of patients were suspicious, defensive, fearful, with delusional ideas of bodily change and sexual preoccupations. With drug treatment they became more withdrawn and denied their illness even more vigorously with lessened fearfulness and lessened suspicion.

The second group of patients were angry, demanding, felt unjustly confined, and had persecutory delusions but without fearfulness or depression. They were quite hyperactive. Following chlorpromazine, their anger and disturbed behavior dropped abruptly and their hyperactivity disappeared. They showed insight into their illness, actively participated in the hospital routine, and socialized well with other patients.

Although both groups changed strikingly, the quality of the improvement in the second group was clearly superior to that in the first.

A grant-supported group at Spring Grove State Hospital, Maryland, had last year completed a comparison of several older phenothiazine derivatives in acute schizophrenic states. They are at present continuing their work investigating a series of new phenothiazine derivatives including thiopropazate, trifluoperazine, thioridazine, and fluphenazine. Since this study shares many design features and rating instruments in common with the Psychopharmacology Service Center's nine-hospital collaborative study, the results of the two studies should be generally comparable. In addition, this group has been helpful in providing facilities for the pretesting of instruments now in use in the special nine-hospital collaborative study, and is actively participating in an assessment of rating instruments to be used in the proposed follow-up phase of the study.

An interesting study of a phenothiazine derivative, perphenazine, in the treatment of emotionally disturbed juvenile delinquents in a training school environment, has recently been reported by grant-supported investigators at Johns Hopkins University. The results illustrate the complexities of some types of drug evaluation. Boys resident in one cottage were randomly assigned drug and placebo, while those in another cottage received no special treatment of any sort. The major finding was that all boys in the treatment cottage, whether on drug or placebo, did much better than those in the nontreatement cottage. Further, after the study was terminated, the drug-treated group appeared to do somewhat less well than the placebo-treated group. The usefulness of drugs in the treatment of emotionally disturbed delinquents is far from demonstrated, although the desirable effects of special studies or special attention are suggested.

Antidepressive drugs

Two three-hospital collaborative studies of the efficacy of drugs in the treatment of depressed patients hospitalized in State mental hospitals are in progress. A grant-supported study at Rutgers University, in cooperation with the New Jersey State hospital system, had already shown iproniazid to be superior to placebo and different from, though not superior to, electroconvulsive therapy in the treatment of depressed women. Further studies on imipramine have now revealed the drug to be significantly superior to placebo, and slightly superior to electroconvulsive treatment in depressed women in this same age range. In contrast to the monoamine oxidase inhibitor, iproniazid, imipramine does not have any specific stimulatory effect on psychological functioning. Its efficacy in the treatment of depression appears to occur through simple alleviation of depressive symptoms rather than through any positive stimulatory effect.

This finding is at some variance with results reported from a similar grant-supported study being conducted on depressed patients of both sexes and all ages at three Massachusetts State hospitals. The study compares imipramine, two newer monoamine oxidase inhibitors (phenelzine and isocarboxazide) and electroconvulsive therapy. Preliminary findings suggest that the overall effectiveness of electroconvulsive therapy is significantly greater than that of the least effective drug, isocarboxazide, with phenelzine and imipramine being intermediate in efficacy. Additional data on ECT, phenelzine, and imipramine are now being collected to permit a detailed analysis of differential effects of, and indications for the use of, the three treatments.

A similar grant-supported study at Creedmoor (New York) State Hospital comparing phenelzine, imipramine and a newer MAO inhibitor, tranylcypromine, has yielded preliminary results showing a slight superiority of tranylcypromine over the other two drugs. The difference may be due partly to the superior response to this drug observed in cases of schizophrenic psychoses with prominent depressive symptoms. This subgroup of patients showing major depressive symptomology constitutes about a fifth of the patients included in both the Massachusetts and Creedmoor studies. It was excluded from the New Jersey study, which may account in part for the differences in the results reported.

The diversity in results and the preponderence of lower socioeconomic groups among the State hospital depressed patients indicate the need for a special collaborative study utilizing a broader group of depressed patients.

Two interesting side studies have been reported by the Massachusetts group. One of these clearly showed that many of the side effects reported in the clinical literature as resulting from antidepressant drugs actually exist as symptoms of depression before drug therapy is even started. Elimination of such pseudo-side-effects reduces the frequency of real side effects by about one-half. In another study, an analysis of admissions for depressive illness to Massachusetts State hospitals by area of residence showed that rapidly growing communities have a significantly higher incidence of depressive illnesses. These patients are generally not new arrivals, but residents who have lived in their community for an average of 7 years.

Outpatient drug studies

A special study developed by the psychopharmacology service center staff, in collaboration with investigators at Johns Hopkins University and the University of Pennsylvania, has focused on the effects of meprobamate and placebo on anxious neurotic outpatients and the influence of two types of physicians' attitudes. Preliminary results suggest that a high level of of therapeutic ardor in combination with the active drug may produce both the best therapeutic response and the lowest number of patients dropping out of the study. Final analysis of the completed study in the summer of 1962 should throw light on the conflicting findings from controlled studies of meprobamate, appearing in the scientific literature. It may well be that a positive, enthusiastic therapeutic attitude on the part of the physician is necessary for the efficacy of this drug to become manifest.

A subsequent special study is being developed to evaluate the effectiveness of a newer tranquilizer—chlordiazepoxide—in neurotic outpatients, as influenced by the patient's perceptions of their physicians' attitude toward the drug.

A separate study at the University of Pennsylvania is showing that psychiatric patients coming to the general medical outpatient department differ significantly in response to drugs from patients coming to the psychiatric outpatient department—both in the degree of improvement produced by drugs and the incidence of side effects. This study is being extended to include patients seen in private practice.

A British investigator, using an extensive panel of general practitioners, has shown phenobarbital to be superior to placebo in the treatment of acute anxiety symptoms and dextro-amphetamine inferior to placebo in the treatment of mild depressive states. He is now proceeding to study newer drugs such as chlordiazepoxide and phenelzine, as well as an older, but very widely used combination tablet containing both a barbiturate and dextro-amphetamine.

Drug usage information

A contract with Lea Associates, Inc., for information on the use of psychotropic drugs by a representative nationwide sample of physicians in private practice resulted in a two-volume report providing extensive data on utilization of these agents in office practice. Among the more significant findings, two may be noted: (a) physicians in private practice use conventional psychotropic drugs for a wide variety of disorders, of which only 28 percent are diagnosed specifically as mental disorders; the remaining include circulatory, digestive and other medical disorders; (b) a disproportionate number of female patients (69 percent) are being treated with psychotropic drugs.

The results of the study were supplemented by a thorough analysis of drug usage at the Group Health Association of Washington, D.C.; and a similar analysis was conducted by PSC staff using the records of the Health Insurance Plan of New York. Findings indicate that essentially the same factors determine the incidence of psychotropic prescriptions within a prepaid group medical practice as in private medical practice.

The information obtained from both of these studies is useful in that it provides for the first time reliable data concerning present utilization of psychotropic drugs outside the mental hospital, which can further be used in the future to follow trends in drug use.

BASIC RESEARCH STUDIES

Studies of drug effects in normal subjects

Controlled experiments on normal subjects were carried out at Seton Hall College of Medicine and Boston University School of Medicine during the past year. These studies were designed by the PSC staff to investigate the combined effects of pharmacological and psychological variables operating simultaneously, permitting the determination of the interaction of these two kinds of variables. Consistent data have now been obtained indicating that different expectations of subjects participating in drug studies can markedly affect their response to de-amphetamine and placebo, as measured by subjective response and psychomotor performance. It has further been shown that under certain conditions the operation of a powerful psychological variable can override pharmacodynamic action to the extent that the drug appears to reverse its true action. For example, an instructional set (i.e., anticipatory expectations conveyed by the experimenter to the subjects) can significantly potentiate or inhibit the pharmacological effects of 10 mg. of de-amphetamine on various measures of mood, subjective state, psychomotor performance and autonomic response. Under one expectation, amphetamine subjects show elevated mood and autonomic response along with improved psychomotor performance; under another amphetamine subjects may show depressed mood and autonomic response and impaired performance relative to placebo subjects. These results suggest that the traditional concept of stimulant and depressant drugs can be decidedly misleading in psychopharmacology, since it appears that behavioral action of some psychotropic agents may in part depend upon the psychological state of the subject at the time of adminstration. A further implication is the need for greater standardization of clinical evaluations and control of certain socio-environmental conditions in the search for new drugs effective in nonpsychotic populations.

Reports from a grant-supported group at the Massachusetts Mental Health Center have underlined another important dimension in the study of drug effects in normal subjects. Two clearly different groups of normal college student volunteers, one athletic and extroverted and the other more intellectual and introverted, have been shown to differ strikingly, both in their reactions to tranquilizers and to the psychotomimetics—psilocybin, LSD–25 and mescaline. Under these drugs both personality types showed distortions of body image, visual illusions and hallucinations and disorganized thinking. However, the athletic subjects showed little disturbance of psychomotor performance, minimal impairment of mental functioning and learning and few somatic complaints, while showing marked physiological changes. On the other hand, the more introverted subjects showed little physiological change, many somatic complaints, intense mental confusion and psychomotor retardation.

Another contribution to the methodology of drug studies, emphasizing the effects of expectations produced by the administration of tablets, was reported by a group of investigators associated with the Society for Medical Ecology working with subjects drawn from a Veterans' Administration domiciliary in Martinsburg, W. Va. The Psychopharmacology Service Center's contract-supported biometric laboratory at George Washington University participated in the design of the study and analysis of data. These elderly subjects were divided into four groups—one received orange juice alone; one received 10 mg. of dextro-amphetamine dissolved in orange juice and were unaware of receiving any medication; while the other two groups received orange juice alone, and then, respectively, a capsule containing 10 mg. of dextro-amphetamine or an inert placebo. The findings showed an adverse drug effect on mood and a positive placebo effect on mood, with the overt placebo subjects feeling best and the subjects receiving dextro-amphetamine concealed in orange juice feeling least well.

A significant contribution to the understanding of the effect of psychotomimetic agents has been reported by a grant-supported group at the University of Illinois.

They have reported that dosages of LSD, producing bizarre visual experiences including hallucinations in normal subjects, also produce obvious changes in the electrical response of the retina of the eye to light. In order to determine whether this effect was the crucial site of action of LSD in producing hallucinations, the group also studied blind, eyeless individuals and found that in those who had once had vision, LSD produced hallucinatory visual experiences, proving that the electrical changes produced in the retina by LSD are not necessary for the elicitation of drug-induced hallucination.

A group at the University of Cincinnati have reported imipramine to decrease the frequency of dreaming in normal subjects, but to increase the amount of hostility expressed per dream, a change not produced by either the phenothiazine, prochlorperazine, or by phenobarbital. This work may contribute to the better understanding of how the antidepressant drug, imipramine, acts in abolishing bed wetting in enuretic children.

Animal studies

Grantees at Harvard University and at the University of Chicago have contributed excellent recent reviews on the effects of drugs on animal behavior. The investigator at Harvard concludes that the efforts of chlorpromazine are best explained as a reduction of the responsivity of the organism to environmental stimuli. He also notes that, although clinical evidence supports the hypothesis that chlorpromazine acts through decreasing anxiety and fear-motivated behavior, the animal work to date shows the drug to depress both fear-motivated behavior and also behavior directed toward positive goals, such as obtaining food or water, without showing either type of effect to be predominant.

Continued explorations of the effects of psychoactive drugs on various types of behavior, including stimulation of "pain centers" and "pleasure centers" in the brain, and even more basic studies of drug-induced changes in neurophysiological activity and brain biochemistry are actively underway. However, emerging findings continue to be both complex and fragmentary. One interesting approach to the study of drug-behavior interactions has been developed at a grant-supported unit at the University of Maryland. Complex behavioral sequences, where the behavior of the animal during any one phase of the experiment can affect the next set of conditions to which it is exposed, are being explored to see if the increased complexity of the behaviors required of the animal will lead to more sensitive measures of drug effect. Heretofore much research on the effects of drugs on animal behavior has been concerned with simple behaviors, such as pushing a lever to avoid a painful shock, a mechanism so simple and so easily learned as to be relatively insensitive to the effects of clinically relevant dosages of psychoactive drugs.

One study involved the effects of chlorpromazine on the social and behavioral development of puppies reared in relatively complete social isolation. It was observed that, even under these adverse conditions, the drug had no detectable effect on the puppies' growth or behavior.

One of the major goals of the PSC has been the encouragement of the use of improved methodolgy in animal behavioral studies with psychoactive drugs. A A special staff report, "Behavioral Research in Preclinical Psychopharmacology—Issues of Design and Technique," embodying detailed suggestions for research workers utilizing animal screening techniques for the psychoactive drugs, was published in the September PSC bulletin.

Drug metabolism

The considerable unexplained individual variability in patient response to psychoactive drugs suggests that drug metabolites and individual variations in the way in which drugs are absorbed, metabolized and excreted may play important parts in enabling these clinical phenomena to be understood and more effectively handled.

For this reason the PSC has been particularly active in stimulating research on drug metabolism and has held annual workshops attended by the 11 grantees now working in this area. In addition, the contract mechanism has been utilized to support the synthesis of the several hydroxy derivatives of chlorpromazine and related compounds which have been tentatively identified in the urine of both patients and animals, but have not as yet been synthesized or pharmacologically studied. It is possible that, as in the case of the desmethyl metabolite of imipramine, these metabolites may be pharmacologically more active than the parent drug.

In addition to this synthetic work, contracts for the development of better laboratory techniques for the identification and quantitative measurement of both drugs and metabolites in biological fluids (blood, urine, spinal fluid) are under negotiation. These will utilize both conventional chemical approaches as well as newer techniques such as gas chromatography which appear particularly promising. In addition, a grantee at Varian Associates is utilizing a unique facility for the analysis and characterization of these polar compounds through the electron paramagnetic resonance approach, in close collaboration with an experienced biochemist with excellent access to clinical material. The coming year should see increasing productivity of this aspect of the program utilizing a flexible combination of grants, contracts, and staff activity to achieve advances in this important area.

Psychotoxic effect of schizophrenic blood

Considerable interest over the past few years has been focused on the possible existence of a psychotoxic substance in the blood of schizophrenics. Although many conflicting reports have appeared in the literature, a recently published report from grant-supported investigators at the Worcester Foundation for Experimental Biology and the Protein Foundation (Jamaica Plain, Mass.) notes the considerable consensus existing between four independent groups of investigators concerning the exact blood fraction in which this substance occurs and further describes the active substance to be a small molecule bound to protein and distributed over several protein fractions but maximally associated with a specific alpha globulin fraction . The extreme instability of this substance, which loses activity in a matter of hours and is destroyed by freezing, probably accounts for some of the earlier unsuccessful attempts to demonstrate its existence. These investigators report success in maintaining the activity of this substance, as measured by its effect on rope climbing time in the rat, by keeping it in an atmosphere or hydrogen gas.

The general unanimity of the findings of the Worcester group with those of a grant-supported group at the Lafayette Clinic in Detroit and with those of workers at Tulane and at the laboratories of Merck, Sharpe & Dohme at West Point, Pa., was evident at a special meeting of these workers organized by the psychopharmacology study section in the spring of 1961. The opinion of the study section members attending this meeting was that a real psychotoxic substance did exist in the blood of schizophrenic patients. Whether this substance was truly specific to schizophrenic patients or was a nonspecific abnormality associated with stress or with other disease states was judged to be less clearly established.

METHOD DEVELOPMENT AND DATA ANALYSIS

Method development

Two methods for use in clinical drug studies have been developed within the Psychopharmacology Service Center. The first, the Clyde Mood Scale, is a well constructed list of adjectives relevant to mood usable by both subjects and by observers to describe emotional states. It is being widely used in a variety of studies including the nine-hospital collaborative study and all of the studies of drug effects in normal subjects described above.

The second set of instruments, the Katz Adjustment Scales, provides detailed information on the social adjustment of psychiatric patients in the community. It utilizes information both from relatives and from the patients to determine degree and type of psychopathology, level of social functioning and satisfaction with social functioning on the part of both patients and their relatives. It has been shown capable of discriminating effectively between well and poorly adjusted patients followed in an aftercare clinic. A second validation study is now in progress under a special grant at Spring Grove State Hospital.

The detailed data on five different approaches to measuring drug-induced change in schizophrenic patients will be available from the collaborative study of phenothiazine derivatives described above. Detailed analysis of these data will permit substantial revision of the measures to make them more efficient and sensitive to drug effects.

Work is also underway on a comprehensive critical review of the existing literature on clinical rating instruments and the preparation of a special handbook making detailed evaluative information on all major rating instruments available to clinical investigators. This work is being carried out under a special grant to the Society for Medical Ecology.

Special staff work in collaboration with the contract-supported biometric laboratory at George Washington University is utilizing data on relatives' descriptive ratings of newly hospitalized patients as the basis for a reexamination of diagnostic subgroupings within schizophrenic, by means of advanced statistical approaches to the mathematical grouping of individuals. It will be possible to compare patient types as seen by relatives with those developed from psychiatrists' ratings of the same patients using the same statistical procedures.

This work will also be utilized as part of a broader program for developing predictors of drug response in schizophrenic patients. Close collaboration between the Psychopharmacology Service Center, the biometric laboratory, and VA collaborative study unit at Perry Point VA hospital will permit maximum benefit to be derived from the work of both groups.

The biometric laboratory

The PSC staff has continued to provide consultative service and to carry out statistical analysis on certain of its projects. However, the large majority of its needs in data analysis are presently handled under contract with the biometric laboratory of George Washington University.

The biometric laboratory has been in operation for slightly more than 1 year. It is now fully staffed and equipped. Its prime objectives are to assist in the planning of research and analysis of data for the Center and for NIMH psychopharmacology grantees, to improve measurement devices and statistical techniques for use in drug research, and to conduct a continuing study of the usefulness of computers for solving problems in psychopharmacology.

The laboratory has prepared and assembled a broad selection of computer programs that deal with the prime statistical techniques involved in drug research. These techniques can be classified within the general categories of correlation, discriminant function, and analysis of convariance. In order to provide maximum flexibility and efficiency in reporting results, computer programs have been developed that will permit the laboratory to make use of the IBM 650 and the Honeywell 800 at NIH, the IBM 7090 at CEIR in Washington, and the Univac 1105 at the University of North Carolina. These machines are available to the laboratory and have been used in various phases of the data analysis operations.

Planning and data analysis

The laboratory is devoting about 20 percent of its capacity to the PSC nine-hospital collaborative study. This phase of its operations requires the application of a diversity of statistical techniques and computer programs. In addition to the collaborative study, the biometric laboratory has assisted some 45 investigators in some phase of data analysis during the past 6 months. The amount of assistance ranges from writing a simple computer program for one investigator to a fairly extensive analysis of large amounts of data for another. For example, a group at Hillside Hospital has in progress a clinical drug study that involves two different drugs (a standard antidepressive and a standard tranquilizer), a variety of behavioral rating measures, psychological performance tests, and electrophysiological measurements. Their interest is in whether the drugs actually do produce different effects in the same kinds of patients, which types of patients are likely to benefit from the different drugs, and whether the drugs produce consistent effects on the different types of measures. All of these data are being analyzed at the biometric laboratory.

The data analysis function is not confined to the clinical area. The laboratory has also been assisting in projects at the preclinical and early clinical levels.

Improvements of methods and statistical techniques

The laboratory is working closely with PSC staff on the development of the social adjustment scales and has carried out the major analysis with regard to these instruments. As noted, it continues to refine and analyze the applicability of the Clyde Mood Scale. Its analysis of test data in the collaborative study will permit a comparison of the sensitivity of the various rating scales used. This analysis is in progress. The laboratory will also be involved in assisting the investigators working on the special grant for rating scale evaluation recently awarded by the NIMH. With regard to the diagnostic typing problem noted in a previous section, the laboratory is presently experimenting with new statistical techniques for meeting this problem.

Plans for future methodological development include seeking more efficient computer methods for analysis of electrophysiological data. EEG recordings, for example, have proven to be highly sensitive to drug effects. At present, many of these data are poorly analyzed because of the difficulty in handling it quantitatively. The laboratory has done an extensive analysis of available methods for the processing of electrophysiological data and arrived at specific recommendations for utilization of a highly accurate analog-to-digital converter and a small computer to provide continuing centralized service to as many as 40 investigators working with data of these sorts.

SCIENTIFIC INFORMATION ACTIVITIES

The scientific information unit has had the most active and productive year in its brief history. The volume of work and amount of service have increased greatly, but with a slightly larger staff, better trained personnel, and some improvement in procedures, the unit has been able to handle most of the many demands put upon it.

The increased work and additional functions have covered the whole range of activities performed by the Unit to achieve its goal of facilitating communication of scientific informaton in psychopharmacology. This program, it should be emphasized, is not limited to library and bibliographic services, but is designed to facilitate communication in all possible ways.

Users

The information unit has continued to serve the scientific community. Its users are scientists and clinicians engaged in psychopharmacological research, and the information collected and disseminated is oriented toward the needs of this audience.

One way of estimating the number of scientists to whom information has been disseminated is in terms of the number on the PSC's "roster of psychopharmacologists." This roster is made up of scientists from many disciplines—psychiatry, psychology, physiology, pharmacology, biochemistry—who have asked to receive materials distributed by the Center. As of December 1, 1961, there were slightly over 4,000 names on the roster. Names are being added at the rate of about 100 a month. About two-thirds of the roster is made up of scientists and clinicians working in the United States; the other third are scattered in 52 different countries throughout the world, with most of them in England, Germany, Canada, France, Italy, and the Scandinavian countries. However, there are also quite a few from the Soviet Union, Poland, Czechoslovakia, and other countries in Eastern Europe, some representation from Latin America and the Far East, and a scattering from the Middle East and Africa. The staff has carried on a surprisingly active correspondence with these scientists. Those from outside the United States seem to be unusually appreciative of the services. Scientists on the roster are also very cooperative in providing the Center with information about their activities and research; many reprints and manuscripts, as well as letters, are received every day. Needless to say, in spite of this wide usage by scientists generally, the PSC staff itself probably benefits most from these activities. The staff of the Information Unit has assisted all the other programs of the Center by providing all kinds of background information and auxiliary services.

Psychopharmacology collection

In December 1961 there were over 17,000 reprints, manuscripts, monographs, books, and other materials in the psychopharmacology collection. Efficient maintenance of this collection, including acquisition of the documents, organizing, shelving them, charging out documents, and reshelving is no small task. As the collection grows larger and its use more extensive, particularly because of increases in PSC staff, taking care of the documents is becoming more difficult. Searching and selecting the literature during the past year has been done partly by staff of the Information Unit and partly by the staff of Psychopharmacology Abstracts. At the present rate of expansion, some provision for microreproduction or discarding part of the collection will probably be necessary soon.

During 1961 the staff continued to do all the indexing and coding of materials in the collection. The index is relatively detailed and permits retrieval along several different dimensions. The systems for handling material for storage retrieval include primarily an author index, subject indices on punched cards, and a system using an automatic typewriter and punched cards and paper tape. A major accomplishment during the year was the transfer of several thousand reference citations to edge-punched cards and tape. These references can now be printed out automatically whenever they are needed.

The staff has been actively interested in all new methods of documentation. Two review articles are now in process, one on Problems of Documentation in Mental Health and the Behavioral Sciences, and the other on Contributions of Psychology to Documentation.

The translating program and international aspects of the Unit's work were improved during the past year, mostly by the appointment of a scientific reference analyst with knowledge of several languages. Translation of articles in the Slavic languages proceeded well; the PSC has now translated all Russian psychopharmacological articles appearing in 1960, has abstracts of those for 1961, and has a large number of translations from earlier years. These translations were sent to several investigators who requested them and are, of course, available to others who may need them. The PSC is providing much of the material to a grantee who is reviewing the Soviet psychiatric literature.

Publications

The Psychopharmacology Service Center Bulletin, a newsletter designed to provide informal, rapid communication of all kinds of information to psychopharmacologists, was published five times during 1961. The March issue contained a complete list of all NIMH psychopharmacology grants, with annotations and an index. Preparing this list was an important and time-consuming activity of the Unit, but its constant use, both by staff and others, seemed to warrant the effort. Other issues contained a wide variety of articles and reports of current interest. All writing and editing of the Bulletin is done by the Information Unit staff.

Psychopharmacology Abstracts, a new abstracting service, emphasizing wide coverage and speedy publication, began in March 1961. It is being prepared under contract with a firm specializing in production of abstract journals. Because this work was launched in 1961, it required a great deal of time on the part of Information Unit staff for such activities as advising on the selection of articles for abstracting, checking accuracy of the abstracts, and general monitoring of the work.

Other informational services

During the year many special bibliographies and other informational materials were prepared. It seems safe to say that for every review article in psychopharmacology published or in preparation during 1961, the PSC provided bibliographic and other assistance. The number of inquiries increased by about 50 percent. These inquiries ranged from relatively simple, factual questions that could be answered quickly, to requests requiring detailed and often complex bibliographic services, to problems that had to be handled by a staff member competent to make judgments and evaluation. The Unit is fortunate not only in having well-trained medical librarians who are thoroughly familiar with the subject matter of psychopharmacology, but also a medical officer responsible for liaison with members of the medical profession.

CONTRACTS AND GRANTS

In line with the policy decision made in 1960 to maintain a relatively small core staff in the information unit and to arrange for much of the work to be done under contract or grant, several such projects were put into effect in 1961.

As mentioned before, Psychopharmacology Abstracts is being published under a contract that calls for searching the literature, writing abstracts, providing the PSC with a copy of each article, and publishing a monthly abstract journal.

A 3-year special grant was awarded in June for the development of a new system of indexing and for the actual indexing of all materials in the PSC collection. A thesaurus of index terms, which should be a significant contribution to the whole field of documentation in mental health, is now in preparation. Planning and consulting with this grantee constituted one of the major activities of the staff during the latter half of 1961.

A contract to prepare a handbook of animal psychopharmacology, based on the literature for 1960, was negotiated and work in now underway.

The special grant for bibliographic research was in its second year during 1961. This has been an especially successful endeavor. Annotated bibliographies covering insulin, CO_2, Metrazol, and other such therapies will soon be published, and will serve as basic reference material to the PSC and other psychopharmacologists.

As of December 1961 a contract with a firm specializing in translations of scientific material was in final stages of negotiation. This contract will strengthen the PSC's translating program and aid materially in making it a worldwide clearinghouse for information in psychopharmacology.

HALFWAY HOUSE

Mr. FOGARTY. What do you think about the halfway house?

Dr. FELIX. You mean for psychiatric patients?

Mr. FOGARTY. Yes.

Dr. FELIX. I think it is one of the really fine developments of the last few years.

Mr. FOGARTY. Does this help you get patients out of an institution more quickly and get them back into society?

Dr. FELIX. Yes, this is true. The usual course you find is a patient comes to a hospital and stays for a minimum of time necessary to take maximum benefit from the hospital. Then he may go on to what we call a day or a night care program.

He may go to work in the day and come back to the hospital at night, or stay in the hospital in the day and go home at night, or go to a halfway house sort of situation.

In many cases the next step will be that he is ready to leave the hospital environment entirely, but he is not yet ready to go back home and assume full activities. So he will go to a halfway house type of situation in which he will go to work and come back there in the evening. He will be in group therapy sessions with people on the staff of the halfway house. He will probably still be on some drugs.

He moves from there back out into full participation in the community.

Mr. FOGARTY. He goes back home then?

Dr. FELIX. Yes, sir.

HOMEMAKING SERVICES

Mr. FOGARTY. What do you think about the homemaking service to provide home care for some of these people?

Dr. FELIX. This is working out very successfully. They are doing this in a number of States. Georgia is doing this rather extensively now through their public health nurses, in which this is particularly true of women, mothers and wives. They will go home and the homemaker service comes in and helps to relieve her of some of her responsibilities, get her going again, and stands by for advice and support.

Mr. FOGARTY. This also helps to get them out of the hospital more quickly and back in the home, doesn't it?

Dr. FELIX. That is true. All of these we list under what we call Community Service, which should be significantly expanded and there should be more demonstrations of this in more parts of the country. We are pushing this as rapidly as we can.

Mr. FOGARTY. Sometimes I think if you gave it some name other than Community Services it might be more attractive and more States might be picking it up.

Will you provide for the record a statement on home care and the homemaker program.

Dr. FELIX. Yes, sir.

Mr. Fogarty. Tell us what you think about it, how it is working, and expand on what you think the results will be.

(The requested information follows:)

Home Care of the Mentally Ill

Home care of the mentally ill is seen as an important component of comprehensive community care. Home care may be arranged as an alternative to treatment in a general hospital or a mental hospital during the acute phase of illness, during the convalescent period following hospitalization, or as a means of long-term care for the chronically disabled. In order to make home care possible, there must be available medical, nursing, and social service consultation, and, where needed, financial assistance to help in the basic maintenance of the patient and to purchase needed medications. Home care may take place in the patient's own home, halfway house, or in foster homes. There is an increased use being made of foster care prior to or instead of admission to a hospital, particularly for geriatric patients and for the mentally retarded.

Homemaker services are an essential component of the care of patients in their own homes. The homemaker may make it possible for the children to remain in the home while the mother receives treatment and the father continues to work to support the family. Homemakers can aid former mental patients to resume household tasks and responsibilities. With older patients, a part-time homemaker may be the ingredient that will allow the person to remain at home rather than to be hospitalized. "Meals-on-wheels" also supplement those part-time homemaker services. "Meals-on-wheels" is a service which provides patients with nutritious, well-balanced meals in their own homes. The Visiting Nurse Service of Rochester and Monroe County, N.Y., provides such services.

Home care services, including homemaker services may be offered by a comprehensive community mental health service, a psychiatric service in a general hospital, or a local health department. Welfare agencies and voluntary family service agencies also may provide homemaker services. A few State hospitals located in urban areas have also experimented with these services.

The various networks of programs of aftercare services for patients discharged from mental hospitals provide supervision for many persons in their own homes. Other patients, through the help of aftercare services, are able to live in foster homes as is being practiced in Maryland, California, Indiana, and North Dakota. In both instances, patients are able to live in more "normal" surroundings, be near to their family and friends, and experience less isolation and disruption of their daily lives. In all parts of the country, there is an ever-increasing interest in aftercare services as seen in Michigan, Mississippi, Ohio, Georgia, Maryland, Montana, Minnesota, Kentucky, and North Carolina. The Mental Health Project Grants program has supported over 45 studies and demonstrations in this general area of concern.

There is a growing trend in many communities to provide alternatives to hospital care or to shorten the period of hospitalization. Family involvement in the care of the patient has been and is an important consideration. The family's willingness to take care of the patient at home, while he is receiving outpatient treatment, is an important determinant in how long the patient has to be hospitalized. Families are increasingly encouraged to visit patients in the hospital (in the past, families were not allowed to visit the patient for many weeks after hospitalization), and are encouraged to take the patient home on weekends. Nursing personnel and/or social workers may hold group sessions with family members to help them discuss questions about "home management." A demonstration, "Family Treatment of Schizophrenia in the Home," is underway in Philadelphia supported by a National Institute of Mental Health title V grant.

Home visiting clinical teams and homemakers' services can make it possible for patients to be cared for in their own homes. The mental health project grants program has several projects that are designed to study the provision of homemaker services to families at the time of admissions of mothers who are leaving young children at home, or to facilitate early discharge of these mothers. Homemaker services are also used for geriatric patients as in North Carolina.

The National Institute of Mental Health has joined with other parts of the Public Health Service and with State mental health programs in discussing the importance of home care, including homemaker services and aftercare. Discussions have been held with both health and welfare agencies at the State and community levels to elaborate on the need of precare and aftercare services. (Example, meeting of voluntary social agencies in the Los Angeles area.) Several general hospitals that provide home care (nursing and medical) for chronically disabled patients are beginning to explore the possibilities of offering the same care to mentally ill patients. The NIMH is encouraging this development. NIMH is also encouraging outpatient psychiatric clinics to assist families in providing home care by working closely with the patients, key family members, the psychiatric inpatient facility, and other key agencies. This frequently means a significant revision of clinic programs, or the establishment of a community care unit. In one demonstration in northern Virginia, a modestly staffed unit has been able to effectively mobilize social and health agencies in the community to extend their caseloads and provide services for mental patients. Families are involved in the planning for the patient and in group discussions, making it possible for many patients to leave the distant mental hospital much sooner.

PREVENTION OF MENTAL ILLNESS

Mr. Fogarty. What are you doing in the field of preventing mental illness?

Dr. Felix. I think we are doing a great deal. I am thinking of how to break it down. We are at the present time working in several States through the school systems in developing better mental health services in connection with the school systems.

We found something rather interesting here——

Mr. Fogarty. Another example would be the training of general practitioners.

Dr. Felix. The training of general practitioners is another. And the work we are dong with Yale and the University of Pennsylvania at the present time in the better training of lawyers in this whole area in dealing with the emotional patient.

Mr. Fogarty. I meant to ask you about the clergy. You gave grants to three denominations—one Catholic, one Protestant, and one Jewish.

Dr. Felix. Yes, sir; we did.

Mr. Fogarty. Where are they located?

Dr. Felix. The Catholic was Loyola in Chicago; the Jewish was Yeshiva University in New York; and the Protestant was Harvard Divinity School, which is a nondenominational Protestant.

Mr. Fogarty. These projects have been termed really worthwhile.

Dr. Felix. They were.

Mr. Fogarty. Because many of the people who are affected talk to their clergyman, whoever he might be; and if they know something about these problems, they can refer them to the proper doctor. Is that working out?

Dr. Felix. That is true. There have been several books published as a result of these projects by each of the three seminaries on how you go about pastoral counseling in this area, how you detect certain kinds of problems.

Mr. Fogarty. You can expand on what you are doing in the field of prevention.

(The requested information follows:)

Prevention

The strategy of the National Institute of Mental Health in effecting a preventive approach to mental and emotional illness is threefold: Through research to devise new approaches to prevention; through training to prepare professional personnel in known preventive methods; and through technical and professional assistance to the States to foster the development of prevention programs.

To date, this research, training, and program development teamwork has had its greatest achievements in decreasing the prevalence of organic mental illnesses such as paresis, pellagrous psychoses, and various other toxic or infectious diseases of the brain. The recent breakthrough in the early detection and preventive dietary management of PKU was made possible by NIMH research. In these diseases, it is more feasible to eliminate or modify the cause of the disease or to prevent exposure to the causative agents. Applying the necessary understandings and tools to specifically prevent some of the functional mental illnesses, such as the schizophrenias, will require completion of research now in progress.

At this time we are more amply equipped with the knowledge, personnel, and program methods to prevent the disabilities and personal disorganization caused by many of the neurotic and minor emotional disorders. In addition to the many prevention programs in the States supported by mental health grant-in-aid funds, the Institute is supporting, through its mental health project grants, the exploration and development of new preventive approaches. Such investigation and demonstrations include: A suicide prevention and emergency service project in California, several programs to prevent emotional disorders in children by working with the family, educating mothers in child rearing, working with "problem-producing families," as well as utilization of preschool or primary grade school screening diagnosis and care of emotionally vulnerable children. Other grants support studies of the preventive impact of adult education, college mental health services, counseling services to the aged, consulting services to community leaders, as well as marital and premarital counseling. Primary prevention of learning disorders, school behavior problems, and school dropout, are being investigated in 10 school mental health projects, while four projects are seeking to validate methods to prevent delinquency by use of approaches utilizing schools, social agencies and health resources.

The development of preventive programs against mental disorders has been speeded by the operation of over 121 technical assistance projects since 1955. Each of these projects have provided the services of national consultants to train key leaders in the mental health programs of the various States in the operations, content, and evaluation of preventive programs. In addition, the Institute is operating demonstration programs to provide examples of preventive approaches to the control of narcotic addiction, alcoholism, phenylketonuria as well as the reduction of school mental health problems. Thus, through the provision of technical consultation, administration of grants, operation of demonstrations, and technical assistance projects, the Institute is providing ways that research knowledge can be utilized and the personnel who have been trained can be given the opportunity to extend preventive services to the public.

SCHIZOPHRENIA

Mr. FOGARTY. You talked quite a bit about the problems of schizophrenia in your opening statement. But if you have a more detailed report, you can supply that for the record.

(The requested information follows:)

SPECIAL REPORT: SCHIZOPHRENIA

INTRODUCTION

Schizophrenia remains a major medical and social problem in the United States. It has its greatest impact on the population during the most productive years of life, thus making it a costly disease in the economy of the country. In full recognition of the gravity of this disorder as a public health problem, the Institute continues to extend its support for research, training, and community service activities which will assist in its diagnosis, treatment, and prevention. This support covers a wide range of studies in basic and clinical research, in the testing of promising therapeutic measures, and in the collection and analysis of trends in mental hospital populations, as well as programs for the advanced training of personnel in techniques of therapy and rehabilitation, and projects in the development of hospital, clinic, and community services for the diagnosis, treatment, and rehabilitation of the mentally ill.

The following report indicates the current support and conduct of research under NIMH auspices which can be said to be directly concerned with schizophrenia.

THE RESEARCH GRANT PROGRAM

During fiscal year 1961, approximately $9.3 million was awarded for some 276 research investigations directly concerned with schizophrenia to be conducted in hospitals, clinics, universities, and other institutions throughout the country. At the time of this writing, it is estimated that $9,900,000 will be awarded in fiscal 1962 for research on the many problems relating to schizophrenia. Included among these awards are funds for the establishment of three clinical centers with a total support for the first year of approximately $665,000.

The specific areas of investigation are to a large extent influenced by changes in emerging concepts of the etiology of this disorder. Many research investigators today feel that it is unlikely that any single cause of schizophrenia will be identified but rather that the condition results from the interaction of multiple biological, psychological, and social factors with the role of each of these factors varying from patient to patient. Investigations are therefore being supported not only in psychiatry but in the areas of psychophysiology, neurophysiology, genetics, endocrinology, biochemistry, psychology, sociology, and epidemiology. Findings from these basic investigations are being related to understandings from dynamic psychiatry in the hope that a conceptual scheme will develop which will allow investigators to view the multiple factors involved in a single framework to accommodate all the findings and permit better understanding of their relationships.

Psychopharmacology

Two new phenothiazine derivatives, carphenazine and thioperazine have emerged during the past year which are reported to be quite effective in the treatment of acute and chronic schizophrenic states. A currently grant-supported investigator has suggested that there is a spectrum of clinical efficacy running from strong antipsychotic potency in several phenothiazine derivatives through to strong antidepressive activity in the imipramine-like drugs, with compounds intermediate in chemical structure such as the thioxanthenes possessing varying degrees of both properties.

An interesting tranquilizing drug of totally different chemical structure, haloperidol, has been reported by European investigators to be effective in the treatment of acute schizophrenic states and to produce neurological side effects similar to those observed with the phenothiazines. In preliminary studies, American investigators, including several grantees, have been unimpressed with this drug's effectiveness. A definitive comparative controlled study comparing this drug with a potent phenothiazine, thiopropazate, has been completed under an early clinical drug evaluation grant to Stanford University supporting collaborative work in several Veterans' Administration hospitals. The data are now under analysis.

In the late fall of 1960 a program of special grant support was developed by the National Institute of Mental Health in recognition of the need for early clinical drug evaluation. This program is intended to support trials of promising agents to determine their safety, appropriate dose ranges, and side effects as well as to collect preliminary evidence of clinical effectiveness in particular symptoms or syndromes. As is appropriate in terms of the current public health need, the program at present gives major emphasis to the evaluation of drugs useful for acute and chronic schizoprhenics and provides more limited facilities for the evaluation of drugs in depressive patients, nuerotic out-patients, alcoholics, and other special psychiatric diagnostic groups. One unit is focusing upon the evaluation, in children with psychiatric disorders, of drugs already shown to be safe and effective in adult patients. Since psychiatric disorders of childhood respond differently to many drugs (for example, hyperkinetic overactive children are tranquilized my amphetamine), special studies in this particular group are clearly necessary.

There is continuing evidence that drug treatments for hospitalized schizophrenic patients are having a significant impact upon mental hospital populations. Dr. Henry Brill, deputy commissioner of the New York State Department of Mental Hygiene, has recently reported a continuing steady decrease in the number of hospitalized schizophrenic patients in the New York State hospital system over the past 5 years in the face of an increased number of new admissions each year. In addition, he has found that the number of schizophrenic patients continuously hospitalized for 5 years following admission—the hard core of treatment-resistant patients—has dropped approximately 20 percent over the past 5 years. Although other significant changes have occurred in the New York State hospital system during this period, Dr. Brill feels that drug treatment has been a major factor in this dramatic reversal in the steady increase in the number of patients hospitalized every year which had been observed up until 1956.

A grant-supported study by investigators in the California Department of Mental Hygiene of the release rates of male schizophrenic admissions has produced a report which raises interesting questions concerning the mechanism by which this decrease in numbers of hospitalized patients has occurred. In other naturalistic study of male schizophrenic patients who did and who did not receive drug treatment during their initial period of hospitalization, they find no differences in release rates between the drug-treated and nondrug-treated groups. These results confirm an earlier grant-supported study by an investigator at Catholic University who arrived at similar findings on a survey of release rates for drug- and nondrug-treated patients hospitalized at St. Elizabeths Hospital in Washington, D.C. It may well be that drugs, though effectively controlling the symptoms of serious ill schizophrenic patients, may also contribute to a general improvement of hospital milieu leading to better response in schizophrenic patients not so seriously ill as to warrant drug treatment. Further grant-supported work with chronic schizophrenic patients treated in outpatient clinics has continued to underline the utility of drugs in this type of patient. Work at Kings County Hospital in Brooklyn has not only shown that chlorpromazine is much more effective than inert placebo in preventing hospitalization, but that it also produced significantly greater improvement in the social adjustment of patients remaining in the community.

The considerable unexplained individual variability in patient response to psychoactive drugs, the slow response of patients to many of the antidepressants, the highly variable dosages of phenothiazines needed in the treatment of schizophrenic patients, and the highly variable period of continued clinical stability following cessation of phenothiazine therapy all suggest the possibility that drug metabolities and individual variability in the way in which drugs are absorbed, metabolized, and excreted may play important parts in enabling these clinical phenomena to be understood and more effective handled. For this reason the Psychopharmacology Service Center has been particularly active in stimulating research on drug metabolism and has been holding annual workshops attended by grantees now working in this area. In addition, the contract mechanism has been utilized to support the synthesis of the several hydroxy derivatives of chlorpromazine and related compounds which have been tentatively identified in the urine of both patients and animals, but have never been synthesized or pharmacologically studied. It is, of course, possible that, as in the case of the desmethyl metabolite of imipramine, these metabolites might be pharmacologically more active than the parent drug. In addition to this synthetic work, contracts for the development of better laboratory techniques for the identification and quantitative measurement of both drugs and metabolites in biological fluids (blood, urine, spinal fluid) are under negotiation. These will utilize both conventional chemical approaches as well as newer techniques such as gas chromatography which appear particularly promising. In addition, a grantee at Varian Associates is utilizing a unique facility for the analysis and characterization of these polar compounds through the electron paramagnetic resonance approach, in close collaboration with an experienced biochemist with excellent access to clinical material. The coming year should see increasing productivity of this aspect of the program utilizing a flexible combination of grants, contracts and staff activity to achieve advances in this important area.

Considerable interest over the past few years has been focused on the possible existence of a psychotoxic substance in the blood of schizophrenics. Although many conflicting reports have appeared in the literature, a recently published report from grant-supported investigators at the Worcester Foundation for Experimental Biology and the Protein Foundation, Jamaica Plain, Mass., notes the considerable consensus existing between four independent groups of investigators concerning the exact blood fraction in which this substance occurs and further describes the active substance to be a small molecule bound to protein and distributed over several protein fractions but maximally associated with a specific alpha globulin fraction. The extreme instability of this substance, which loses activity in a matter of hours and is destroyed by freezing, probably accounts for some of the earlier unsuccessful attempts to demonstrate the existence of this substance. These investigators report success in maintaining the activity of this substance, as measured by its effect on rope climbing time in the rat, by keeping it in an atmosphere of hydrogen gas. The general unanimity of the findings of the Worcester group with those of a grant-supported group at the Lafayette Clinic in Detroit and with those of workers at Tulane and at the laboratories of Merck, Sharpe & Dohme at West Point, Pa., was evident at a special meeting of these workers organized by the Psychopharmacology Study Section in the spring of 1961. The opinion of the study section members attending this meeting was that a real psychotoxi substance did exist in the blood of schizophrenic patients. Whether this substance was truly specific to schizophrenic patients or was a nonspecific abnormality associated with stress or with other disease states was judged to be less clearly established.

Two methods for use in clinical drug studies have been developed within the Pychopharmacology Service Center. The first, the Clyde mood scale, is a well constructed list of adjectives relevant to mood usable by both subjects and by observers to describe emotional states. It is being widely used in a variety of studies including the nine-hospital collaborative study and all of the studies of drug effects in normal subjects described above. The second set of instruments, the Katz adjustment scales provides detailed information on the social adjustment of psychiatric patients in the community utilizing information both from relatives and from the patients to determine degree and type of psychopathology, level of social functioning and satisfaction with social functioning on the part of both patients and their relatives. It has been shown to discriminate effectively between well and poorly adjusted patients followed in an aftercare clinic. A second validation study is now in progress under a special grant at Spring Grove State Hospital.

Special staff work in collaboration with the contract-supported Biometric Laboratory at George Washington University is utilizing data on relatives' descriptive ratings of newly hospitalized patients as a basis for the reexamination of diagnostic subgroupings within schizophrenia, by means of advanced statistical approaches to the mathematical grouping of individuals. It will be possible to compare patient types as seen by relatives with those developed from psychiatrists' ratings of the same patients using the same statistical procedures.

This work will also be utilized as part of a broader program for developing predictors of drug response in schizophrenic patients. Close collaboration between the Psychopharmacology Service Center, the Biometric Laboratory, and Veterans' Administration Collaborative Study Unit at Perry Point will permit maximum benefit to be derived from the work of both groups.

Psychotherapy

Despite recent advances in psychopharmacology, psychotherapy continues to be a major form of treatment for most psychiatric patients. However, its principal mode of operation remains inadequately defined. To achieve clarification of the nature of psychotherapy, grant-supported investigators are attempting to relate systematically factors in patient, therapist, and psychotherapeutic method to the short- and long-term outcome of treatment. Other investigators are testing the hypothesis that the psychotherapeutic process may be nonspecific and the outcome may not immediately be related to the condition being treated. They are comparing large groups of individuals in subgroups composed of acute schizophrenics, chronic schizophrenics, and normals, one group receiving psychotherapy and the other not. The extent of association is being sought between the disorder and process of therapy among the three groups receiving therapy.

Since free association is recognized to be a crucial variable in psychonalaysis and psychotherapy, investigators are seeking to find to what extent and how personality factors may influence response to the free association test. Personality differences, measured objectively, are being studied in the nonpsychotic individual to investigate a set of issues which grow out of the use of free association in psychoanalysis. These investigators propose to relate objective measurements of personality to patterns of free association in nonpsychotic individuals. The patterns found in this group would then be compared with those found among schizophrenics, thus giving some indication of the principles governing the appearance of particular associations in awareness.

During this past year, a clinical research center has been established under grant support to focus on the objective study of the psychiatric treatment process, including the process of planned therapeutic intervention and the matrix of factors which coexist within a treatment situation and their bearing upon the patient's response. Patients are being studied within six broad categories of inquiry, including clinical psychopathology, psychodynamics, social behavior, cognitive behavior, psychophysiology, and biochemistry, with the hope that this multiple-route type of inquiry into the therapeutic process will eventually make possible a description and definition of psychiatric treatment in psychobiological terms and add to an understanding of the etiology of the disorder.

Hospitalization and rehabilitation

Studies in hospitalization and rehabilitation are, in reality, a link in the chain of treatment procedures. These studies comprise a rounded program to measure the effect of experiential factors, both in the hospital and in the community, which may be significant in contributing to the recovery of the patient, prior to and during treatment, on the one hand, and to the maintenance of recovery after treatment, on the other.

A factor influencing speed of recovery from an emotional disorder is recognized to be the manner in which the patient is handled when the first signs of the disorder appear. Community agencies are, therefore, being studied for their methods of handling cases of deviant behavior in individuals and the speed and efficiency with which individuals who show psychotic symptoms for the first time are directed to an appropriate treatment facility.

The social milieu of the hospital ward has been found to influence the progress of a patient's illness. The psychiatric ward is, therefore, being studied to compare the social settings of different types of hospitals and to measure the value of the social milieu as a treatment resource. In a number of studies, a detailed observational record is being sought of chronically hospitalized mental patients to provide a pool of behavioral data that would help in understanding the particular actions of mentally ill patients and to provide a baseline of behavior from which changes could be measured for other research, such as drug evaluation studies. In some studies, salient features of the social system are being related to the personality systems of the members as measured by objective tests. In others, the environmental contingencies in the ward which govern and shape verbal behavior are being studied in an attempt to modify the pathological verbal behavior found in hospitalized psychiatric patients. Such data are important in relating the presenting symptoms of an individual patient to the social structure of the ward, thus becoming a part of the continuing evaluation of the treatment the patient receives.

With the increasing number of ambulatory patients resulting from success in psychopharmacological treatment, investigators are studying the various factors related to the extrahospital and aftercare setting of the patient. The personal and social adjustments of patients are being observed in community-based follow-up studies to examine the role of pharmacological treatment in the posthospital experience of the patients, the comparative effects of drug and nondrug treatments on the rehabilitation of the patient, rehabilitation to be measured by a wide variety of behavioral measures including a sociological appraisal in relation to family members, psychological appraisal with objective tests, and a psychiatric assessment with ratings on a number of specific scales using computer facilities for analysis of the data.

Relapse control is being tested by providing drug therapy in a day-care facility. The investigator wishes to determine whether recurring psychotic symptoms can be brought under control in a day-treatment center providing intensive pharmacology, whether these patients are able to return to work more quickly than if they were rehospitalized, to gage the length of remission achieved by treatment in a day-care facility and to determine the social readjustment following treatment in such a facility. Thus far, the investigator reports that remission in the day-hospital patients has been achieved rapidly and that such patients are able to return to their jobs far sooner than patients who were rehospitalized. It was also noted that treatment in the day-hospital seems to promote better community adjustment and that patients seen in the day-hospital seem to have learned that they can discuss recurrences of symptoms without fear of being rehospitalized.

The biology and biochemistry of schizophrenia

A large share of the Institute's grant program supports research projects related to the biology and biochemistry of schizophrenia. As many present-day investigators have rejected the belief that schizophrenia is a disease entity of single causation, clues to a multiple etiology of this mental syndrome are currently being sought in genetics, biochemistry, physiology, endocrinology, and other biological and medical sciences.

A wide range of studies is actively exploring, under Institute grant support, the biological and biochemical aspects of schizophrenia. Among these are included studies of the relation of cerebral physiology to functional disorders relation of metabolic patterns to schizophrenia, immunochemical investigations of schizophrenia, studies of the effect of tryptophan of brain function and mental disease, the role of histamine metabolism in schizophrenic patients, the cerebral metabolism of neurohormone precursors, and the pathological chemistry of brain glycolipids and biologically inactive catechols in mental disease.

Although relatively few Institute-supported research investigators have carried out genetic studies of schizophrenia, evidence for a genetic influence in schizophrenia has accumulated from family and twin studies, suggesting that unevenly distributed individual genetic differences may be of considerable importance in certain, not yet specified, schizophrenic syndromes. The Institute has in the past supported twin studies of schizophrenia and currently supports several projects dealing with genetic factors in psychiatric disorders and studies of mating and fertility patterns of schizophrenic families. Among these, support is being given to a unique long-term followup study of a large series of families marked by psychosis. The transmission of mental illnesses from one generation to the next over a span of five generations is being studied for the incidence of psychotic disorders and related phenomena in relatives of patients; the similarities in manifestations in relatives; and, the possible role of environmental factors, birth order effects, and fertility.

A considerable body of research is underway which is based on the premise that schizophrenia is a genetically determined metabolic disease entity, one characterized by alterations in the metabolic pathway for the breakdown of yet unidentified but endogenously occurring compounds. Some clinical and laboratory findings have suggested that as in other metabolic diseases, a basic deficiency may exist, in varying degrees, in different persons so effected. For example, recent research reports have indicated a possible role of neurohumoral amines in mental health and disease, particularly norepinephrine, serotonin, tryptamine, and histamine. It has not been possible thus far, however, to link them conclusively with behavioral states.

Still other investigators have explored urinary aromatic substances in schizophrenic patients, more particularly as to the presence of abnormal indoles. Underlying this approach has been the thesis that if a chemical or biochemical alteration should be related to a disease in some way, it should be reflected in the chemistry of the urine. Again, however, methodological difficulties have hampered this research—many organic substances in the urine are still unidentified; others are present in such minute quantities as to be unidentifiable; many metabolites are also extremely unstable and undergo changes within the urine. Thus far no metabolite has been identified as conclusively characterizing the urine of schizophrenic patients.

During this year a clinical research center is being supported for the study of the biological factors which may be involved in the etiology of schizophrenia. A well-rounded program will be developed in this center of psychiatric research including both basic and clinical research in the biological, psychological, and social aspects of the disorder. These projects include: Biochemical factors in schizophrenia through well controlled studies in blood and urine; effects on schizophrenic behavior and mental states of alterations in specific aspects of brain and body chemistry by substrate loading or enzymatic inhibition; relationship between central biogenic amines and behavior in animals and man; measurement of regional cerebral circulation and metabolism of the brain and correlation with functional state; and regional neurochemistry and correlation with function.

With the greater refinement of instrumentation and the development of ultramicrochemical procedures it may well be possible to resolve the questions raised by the various findings from the biological and the biochemical approach and to clarify their relationship to the etiology of schizophrenia.

Family studies, psychodynamics, and child development

Increasing numbers of research workers are exploring what might be termed a psychogenic theory of schizophrenia—many through studies of the family interaction of schizophrenic patients. Among some of these studies currently supported in the Institute research grant program are research on attitudes of relatives of mental patients, on family interaction, and psychopathology in schizophrenia, on social and individual systems in schizophrenia and on competitive and cooperative social interaction. Although evidence is accumulating on abnormal interaction and organization which often exist in families of schizophrenic patients, no definite proof has yet been offered which would assume such family background to be a directly attributable cause of mental illness.

The prevalence of disorganized thought processes in the schizophrenic patient has raised the possibility that intellectual deterioration is a basic aspect of schizophrenia. Thus far, research has failed to demonstrate the consistent presence in schizophrenics of the kind of mental deterioration that is found in patients suffering from brain damage, for example. Since the point remains controversial, many investigations are being supported in which attempts are being made to develop more refined techniques for measuring those factors contributing to the organization of thought processes.

Some significant differences in perceptual flexibility have been found between groups of schizophrenic, organic, and medical neurotics. In further studies attempts are being made to focus on perceptual tasks with the inclusion of marker variables permitting comparison with other data so as to obtain a finer categorization of patients and a deeper analysis of the mechanisms of the perceptual phenomena. Similarly, differences and similarities in thinking disorders between chronic schizophrenic patients, acute schizophrenic patients, and brain damaged patients are being investigated. Measures being used include degrees of literalness, overinclusive categories and the like.

Objective psychological test data are being compared with clinical psychiatric assessments to measure their concordance and to obtain as specific a measure as possible for diagnostic purposes and for evaluation of treatment. Affect, as indicated by emotional states and the perception of emotions, is being measured on groups of individuals who have been diagnosed by a psychiatrist. The diagnostic category and affect rating as stated by the psychiatrist are being compared with measurements obtained independently on an objective affect rating scale. In another study personality variables (such as empathy, memory, alienation, anxiety and the like) involved in two-person interaction are being analyzed under varying situational conditions. Assessments made by a clinician are then being statistically compared with objective test data.

Many investigations are concerned with the problem of communication in schizophrenia since changes in speech are symptomatic of the disorder. Comparisons are being made of normal and schizophrenic speech under various conditions to estimate the degree to which schizophrenic patients retain the formal characteristics of normal speech. By establishing a curve of the patterns of schizophrenic language the investigators hope to evolve an objective diagnostic test which could also be used to measure the effectiveness of therapy. Other investigators are comparing the verbal behavior of schizophrenic patients and normals, with emphasis on the relationship between conditioned verbal and nonverbal behavior using various schedules of reinforcement. The formal characteristics of schizophrenic speech are also being explored as a possible measure of social deviance. Objective measures of the formal attributes of speech have been devised and are being tested in the hope that they may be used as indicators of the patients' ability to function in society.

In addition to support of research seeking to evolve objective measurements of psychodynamic variables, a program for the study of the basic mechanisms underlying perception in its relationship to personality is receiving continued support as is also a study of time judgment in normal and psychopathologic states. Significant differences have been found between patients and normals with respect to time judgment and attempts are now being made to study the developmental aspects of this judgment. It has already been found that time judgment is distinctly affected by drugs. Thus, sedatives like secobarbitol seem to slow down internal events so that external time appears faster; stimulants have the opposite effect.

Many studies are also under way wherein the psychologist and physiologist are collaborating in order to compare physiological findings under varying psychological conditions. For example, stress and hallucination in perceptual isolation are being studied in order to measure the effect of varying degrees of isolation from simple confinement through sensory deprivation on physiologic function, such as respiration and heart rate. The psychophysiology of perception is being studied through the investigation of the relationship between human perceptual processes and peripherally evoked electrophysiological activity in the cortex. Other such studies are concerned with many aspects of behavioral correlates of neurophysiological variables. Continued collaborative studies of this type may lead to the framework needed to conceptualize schizophrenia.

A number of investigators propose that the etiology of schizophrenia is developmental, having its basis in early life experiences. This concept is being investigated through a number of studies including psychophysiological studies during infancy, the generalized after effects of early traumatic experience, a longitudinal study of normal and pathological personality development, and a followup study of infantile autism.

Basic to the concept that schizophrenia is a developmental disorder is the theory that autism represents the earliest form of schizophrenia. Investigators studying autism in childhood or the problems of children whose worlds are governed by personal needs and wishes at the expense of objective reality, have emphasized the need for clarification of the differential concepts of childhood schizophrenia. It has been pointed out that some children may manifest autistic isolation and autistic thinking yet not be psychotic; others may be both.

To meet this need, support has been provided for the first time this year for the establishment of a clinical research center designed to conduct a comprehensive long-term program of research and treatment involving autistic children. The children show marked speech disturbances and communication problems, a marked lack of emotional control, and an inability to develop minimally satisfactory relations with their parents and siblings. As pointed out by these investigators, efforts at treatment and understanding of this disorder have been discouragingly unsuccessful. It is their objective to develop precise objective descriptions of the behavior of these children, with relation both to the people and the objects in their environment. This fundamental problem has not yet been attacked on a rigorous systematic basis. They also plan to undertake a series of physiological studies to define any possible abnormalties in the nervous or endocrine systems of these children; to study the medical, social and immediate family histories of these children for possible leads to an understanding of the development of their clinical symptoms; and to investigate several possible approaches to the disorder. If this program is able to achieve even only a part of its general goal of finding ways of restoring normal function to children who, by the age of 3 years have already been doomed to futility, it will have made a significant contribution not only to these children and their families; but to society as well.

Other studies related to schizophrenia

In addition to the research areas discussed above, a variety of Institute-supported studies of the cross-cultural aspects of mental illness and of the epidemiology of schizophrenia are contributing to our knowledge of this disorder. A study to develop electronic computer programing for psychiatric research data is also currently receiving support. The aim of this study is not only to develop newer techniques in the use of the electronic computer in mental illness but also to analyze data in an attempt to evaluate the influence of abnormalties of childbirth, including prematurity, bleeding and toxemia, and the posthospital adjustment of psychiatric patients. A biometric approach to prognosis in schizophrenia is being used by grantees with the hope that subgroups of patients will emerge from their study population which will be characterized by more substantial and basic features of schizophrenia than are available at the present time.

THE INTRAMURAL RESEARCH PROGRAM

The magnitude, complexity, and variety of problems inherent in the study of schizophrenia is so great that there are limitless opportunities for both the biological and the behavioral scientist who chooses to work in the field. Many National Institute of Mental Health investigators are concerned with issues directly related to increasing knowledge of schizophrenic processes; others are working on problems which, while not directly related, are fundamental to the understanding of human behavior whether normal or pathological.

Because severely disturbed family relations have been found consistently in schizophrenic patients, one group of workers is concentrating its efforts on ferreting out the character, nature, and mechanisms of the familial disturbance. They are giving special attention to the thought disorder in schizophrenia, a basic feature of the illness which has long been looked upon as a fixed or organic part of the disease. Data produced in these studies are leading investigators to believe that the thought disorder is learned through familial experience of a specifiable kind. This finding challenges directly a major objection to environmental theories of the etiology of schizophrenia.

Family therapy in schizophrenia, already having proven itself a valuable addition to the psychiatrist's therapeutic repertory, is continuing as part of these studies. Of particular value to the medical and scientific community are the data on the advantages and limitations of exploratory family therapy; the indications and counterindications for it; and the technical problems peculiar to it.

The dearth of fully trained psychiatrists, clinical psychologists, psychiatric social workers and psychiatric nurses to deal with the severely disturbed mentally ill has led another group of investigators to embark on a pilot project aimed at secondary prevention by providing skilled counselors for persons who are undergoing psychological stress they cannot tolerate. In this respect they have anticipated the Joint Commission on Mental Illness and Health which recommended in its report of December 1960, that the emotionally disturbed have skilled attention and helpful counseling available to them if the development of more serious mental breakdowns is to be prevented. For the counseling task, the investigators have selected from the community reservoir of untrained people who have aptitude for this kind of work, married women who, around age 40, are looking for a constructive activity outside the home to take the place of child rearing. The recruitment, selection and training phase of the project is nearing completion with encouraging results. The evaluation phase is still in the planning stage.

Social scientists are continuing to examine staff attitudes in a large mental hospital in relation to their effect upon the patients' therapy and progress. A number of identifiable attitude determinants were found by the investigators on this project. These include the social values of individual nursing personnel and the characteristics of wards to which personnel are assigned but, more importantly, both of these together in certain combinations. Findings from this study will be applied in the future to a 10-hospital comparative study initiated by the Psychopharmacology Service Center.

Another social scientist has, as his basic research interest, the relationship between various psychological and social background factors and the regressed chronic schizophrenic patient's reluctance to affiliate with others. Preliminary analysis of data from his work indicate that chronic schizophrenic patients conformed to a pattern found by other investigators among normal subjects in which subjects born in earlier birth ranks were more likely to meet stress in a social manner than subjects born in later birth ranks. This finding led him to study the relationships between birth order and schizophrenia. Preliminary analysis indicates that significantly more of the schizophrenic subjects studied were last born than first born. This difference, however, appears to be entirely due to the subjects from families of four or more. Since it is impossible with the data at hand to separate the effect of birth order and maternal age, a followup study is planned to evaluate the relative effect of birth order and maternal age in schizophrenia.

Studies of the role of heredity and environment in the etiology of schizophrenia have uncovered some interesting points: (1) There are at least two kinds of disorders which carry the diagnostic label of schizophrenia. In one, hereditary factors seem to be contributing almost all the variance. (2) The incidence of schizophrenia is no higher in twins than nontwins, a fact which rules out such a psychogenic theory of schizophrenia as "confusion of ego identity" (according to which high incidence in twins would be predicted). (3) Concordance rates with respect to schizophrenia are higher for female than male pairs and for same-sexed than opposite-sexed pairs of relatives when the familial relationship is primary (parent-child or sibling) but not when the familial relationship is more distant (grandparents, uncle-aunt and nephew-niece, cousin). These data suggest strongly that psychological factors are contributing at least some of the variance to the incidence of schizophrenia.

In preliminary findings from a study of cognitive and perceptual processes in parents of schizophrenics at least one parent from each pair of a small sample evidenced schizophreniclike thought disorders, even though none of the parents had ever been diagnosed schizophrenic or hospitalized for mental illness. Various aspects of this phenomenon are also the subject of intensive study by another research group which is investigating family relations in schizophrenia. In other studies investigators are using methods of reaction time (a function notoriously disturbed in schizophrenics) and psychophysiological recording to study preparatory set and the arousal mechanism in attempts to elucidate some of the underlying psychological processes in schizophrenia.

National Institute of Mental Health scientists have produced evidence which argues strongly against one current theory of schizophrenia; namely, that which postulates a defect in the metabolism of epinephrine with the production of certain abnormal derivatives which might account for the major symptoms of schizophrenia. To test this hypothesis, the investigators carried out a definitive study of the metabolism of circulating epinephrine in a group of schizophrenic patients and in normal subjects. The metabolites in these two populations were found to be qualitatively identical with no evidence for the presence of abnormal metabolites.

Investigators elsewhere have reported findings which suggest the presence in plasma of schizophrenic patients of a factor which alters the carbohydrate metabolism of red cells. On the basis of these findings it has been possible to predict correctly in a highly significant number, the presence or absence of schizophrenia. On the basis of quite a different approach, an NIMH investigator studying the response of free fatty acids to insulin, has also found a reproducible alteration from the norm in a significant number of schizophrenic patients. These studies are being actively pursued with a systematic consideration of the many variables involved in an effort to determine to what extent either of these findings is basic to or characteristic of a subgroup of schizophrenic illnesses or is the result of adventitious factors.

In another approach to the problem, a psychiatrist and internist have collaborated in the clinical testing of a number of amino acids in attempts to elicit mental or behavioral changes which may be characteristic of alterations in specific amine levels. Findings from this study are being evaluated in order to elucidate their significance in the etiology of schizophrenia and the relationships of biogenic amines to behavior.

The development of an evoked response detector by an NIMH electronic technician working with a neurophysiologist has made possible the recording of electrical activity evoked from the cerebral cortex of intact man. Formerly these brain signals, having to penetrate the skull and scalp were lost in the background noise of the electroencephalogram. Studies of evoked potentials in man, made possible by this detector have been carried on in normal subjects in sleep and wakefulness and in schizophrenic patients. Preliminary findings have failed to reveal any abnormalities of evoked potentials in the latter.

In the area of neuropharmacology, collaborative work with St. Elizabeths Hospital continues. Clinicians, nurses, social workers, biological and behavioral scientists all are combining their efforts in the solution of problems which beset investigators when they undertake the conduct of drug trials in a mental hospital setting: e.g., selection of patients; selection of drugs; animal pretrials; selection of experimental design; the techniques of drug administration in a "blind" study; the assessment of side effects; management of adequate laboratory controls; and the comparison of a number of evaluative techniques.

One psychiatrist in this program concerned with social rehabilitation of mental patients has developed an objective measure of the amount and pattern of social contact of a patient in a ward setting. This instrument, after a year of testing, has been found sensitive and useful in quantifying changes brought about by psychoactive drugs and group nursing techniques. It will be further tested in other settings in a multihospital drug study organized by the Psychopharmacology Service Center.

Other psychiatrists and psychologists are studying the quantity of dreaming in nonhallucinating and hallucinating schizophrenics, by monitoring EEG activity and eye movements. The results so far suggest that the amount of dreaming does not differ significantly in the two groups. Additional studies will be carried out on chronic schizophrenic patients in an effort to define and quantify further the parameters of sleep and dreaming.

Biochemists in the program are continuing studies aimed at developing reliable, sensitive, and specific methods for the routine assay of catecholamines in plasma. Only after the syntheses, destruction, and levels of these compounds in brain are accurately measured can the findings be correlated with behavioral state and determination made with respect to whether or not these substances play a role in normal behavior and schizophrenia and, if so, its nature.

Other biochemical studies have been linked to behavioral observations, both in the experimental animal and in man. The animal studies are aimed at establishing the effects of psychotomimetic tryptamine derivatives, and their metabolites, on several types of behavior in various species and at correlating behavioral effects with metabolic variables in the same subject. An attempt is also being made to correlate behavioral effects with chemical structure and the chemical properties of various tryptamine derivatives, and to examine the effects in man of NN-diethyltryptamine. The latter project is intended to provide information on the relationship between the intensity of psychological effects of NN-diethyltryptamine and the metabolism (and especially the rate of 6-hydroxylation) of the drug. Both chronic and acute schizophrenic patients as well as normal volunteer subjects are participating in the study. Data are in process of being collected and analyzed and no conclusions can be drawn at this time.

A variety of other studies being carried out in the area of stress also have significance for research in schizophrenia. Considerable work is being done on endocrine responses in naturally occurring circumstances since these may prove to have special long-range import for the human organism. Because of the high correlation which appears to exist between endocrine functions and observed behavior, much research effort has gone into the development of new and improved methods for measuring the minute amounts of material produced by the endocrine system.

Not directly related but also of importance in the search for new knowledge concerning schizophrenia are studies of psychotherapy and other treatment techniques; studies of developmental processes; of early biosocial growth; of the coping behavior of the late adolescent (his ability or lack of it to adapt to the transition from high school to college); and of other normal processes which are necessary bases both for promoting healthy growth and for evaluating and diagnosing the pathological.

TRAINING

The Institute's support for the training of professional personnel in skills relevant to schizophrenia is maintained as an integral part of the training grant program in psychiatry, psychology, biological and social sciences, social work, and nursing. In addition, a large share of the Institute fellowship program supports the training of scientists in research skills associated with the understanding and treatment of schizophrenia.

BIOMETRICS PROGRAMS

As a part of its total program, the biometrics branch is engaged in measurements of the prevalence and incidence of mental disorders, and relating this information to pertinent factors of demography, socio-cultural environment, and treatment programs. In conjunction with this function, the Institute's biometrics program provides consultative and direct services to State and local departments of mental health. The branch also supports a long-range program to improve and coordinate the flow of statistical data from various sources in the United States.

The expansion of the newer treatment methods, such as day, night and open hospitals as well as psychopharmacology, has led to increased complexities in the interpretation of statistical data, and has emphasized the need for new statistical reporting systems of adequate scope and flexibility. A model reporting area, in which mental health statistics are processed each month, now includes 26 States. Cohort studies of the fate of schizophrenic admissions (among others) have shown wide interstate variations in release, retention, and death rates, as a function of hospital policies. A refinement of a cohort study is now attempting to control some of the variables which contaminate the comparability of the data.

Through the national reporting program on outpatient psychiatric clinics, data are also available on services to schizophrenic outpatients. Approximately 3,000 children and 15,000 adults discharged from 1,001 reporting clinics in 1959 (70 percent of the 1,429 clinics in the country) were classified with a schizophrenic reaction. This represents only 5 percent of the child patients but about one-fifth of the adult patients diagnosed with a mental disorder. In a comprehensive study in Maryland for 1959 conducted by the Institute, it was possible to compute rates of discharge from clinics per 100,000 population.

Not only are biometric data of importance in sensing the distribution and flow of types of mental disorder under various conditions, but it is probable that comparative data will further the refinement and standardization of present-day clinical diagnostic data.

COMMUNITY SERVICES

The responsibilities of the Institute's Community Services Branch include efforts to improve, extend, and strengthen State and local programs for the care, treatment, and rehabilitation of the mentally ill. Professional and technical assistance to State and local programs is provided through staff of the National Institute of Mental Health in headquarters and in eight regional offices. Special staff is available for hospital consultation, group consultative studies, and surveys. The consultation which is provided covers the full range of services for the mentally ill, including services in clinics and general hospitals, mental hospitals, alternatives to hospitalization, and aftercare and rehabilitation in the community.

The growing trend to experiment with the new methods of care and treatment, and to decentralize and develop new devices for the mentally ill in the local community, make it especially important that consultation be available at this time to disseminate the most recent knowledge from research, from pilot projects, and program experience. While consultation is not usually centered only on schizophrenic patients, as has been indicated previously, schizophrenic patients represent a large proportion of the mentally ill in hospitals and in communities.

Besides administering the mental health project grant program, which is focused on the mentally ill, the Community Services Branch is also responsible for the Federal program of grants to States for community mental health services. The Community Services Branch, since 1955, has utilized technical assistance projects to extend consultation and grant-in-aid services to State mental health authorities. Four technical assistance projects have been concerned with followup services to psychiatric patients upon their return to the community. These projects have brought together community and State leaders to determine which services existed and which services should be implemented to aid in the patients' integration into the community. These exchanges of information are reflected in the establishment of the following programs: new and improved methods of broadening mental health services in population centers rather than in rural areas in order to develop branches in State hospitals nearer to big cities; integration of volunteers into treatment and rehabilitation programs of the mentally ill; hospital-community coordination for total patient care; and pilot workshop for law-enforcement officers on problems associated with mental illness.

Application for mental health project grants have continued to increase, not only in terms of the number of projects and amount of funds expended, but in the scope of coverage in terms of areas of investigation and increased geographic distribution. Approximately 90 mental health project grants were awarded which are concerned with mental illness in mental hospitals and 70 with aftercare and rehabilitation.

Three basic approaches have been emphasized in this program: (1) improved hospital care and treatment; (2) improved administrative practices; and (3) improved community mental health programs. Special consideration has been given to projects related to schizophrenia, more particularly new methods of patient care, preadmission services and followup services.

Among some of the current demonstration studies of new or improved methods of care are a day-hospital program for psychotic children, family-centered treatment of schizophrenia in the home, the continuous care of schizophrenic patients and the outpatient treatment of schizophrenic patients with discussion centering around such aspects as handling of crises, patient selection, and the patient in the community.

AGING

Mr. Fogarty. Also give us a statement on your work in the field of aging.

Dr. Felix. I can supply a statement on that, too.

(The suggested information on the aged follows:)

Special Report: Aging

INTRODUCTION

General awareness of the manifold problems associated with increased numbers of older people was heightened by the White House Conference held early last year. It was concerned with many factors ranging from physiological deterioration of the individual to social and economic stresses. The Institute defines its mission in relation to the mental health of the aging population in broad terms. It must, to be sure, be concerned with geriatric mental illnesses which absorb a large and probably disproportionate share of psychiatric facilities; but it is also concerned with the social and psychological aspects of the aging process as such, to delineate, if possible, mentally healthy modes of aging.

INTRAMURAL PROGRAM

Research on aging is carried out in the Institute's Section on Aging and through its collaboration with the Laboratory of Clinical Science and the Laboratory of Socioenvironmental Studies.

Current experimental studies carried out in the Section on Aging involve both humans and lower animals. The facilities of the Section are organized for research on behavioral capacities in relation to age and to concomitant physiological changes. The Section continues to have two primary foci: (1) The gathering and organization of information on behavioral and physiological changes of aging, (2) investigation of impairments in higher cognitive functions in man, and their modification.

A completed analysis of data obtained during the past 2 years suggests that slowing of associative processes and psychomotor behavior observed in the aged tends to have the attribute of general psychological process. That is, whereas young adults tend to show task-specific adjustment of response speed, older persons tend to have a speed of psychomotor performance more characteristic of them as individuals. The principal data on which these conclusions are based were obtained from the use of an apparatus designed and constructed at the NIMH, called the Psychomet.

Because of the implications of the findings and their relevance to psychophysiological changes in the normal adult, the Federal Aviation Agency requested and was granted the use of the apparatus in their current research on aging in civil air pilots. That agency has completed the examination of 160 subjects using the apparatus and the results are now being analyzed in cooperation with the Section on Aging and the Biometrics Branch. Preliminary results indicate significant age trends in the psychological measurements. Surprising is the fact that the trends are appearing in relatively young, healthy, men. The further analysis of the data as well as new studies, will explore possible physiological bases for the changes. Of considerable importance is the suspicion that the observable behavioral changes may precede physiological changes related to health factors that may appear later. These findings pose implications for determining the extent to which behavioral changes of advancing age may be premonitory and predictive of length of life and disease states.

A comparison of two contrasting age groups of adults with respect to their performances on the standard problems programed by the logical analysis device (LAD) revealed a striking impairment of heuristic behavior in the aged. Additional tests with special, simplified LAD problems failed to bring this form of task within the capacities of the older subjects. During the current year, a device for evaluating heuristic processes and logical problem programing was constructed in the section and preliminary observations were made at several levels of difficulty on young and old normal adults, schizophrenics, and children.

It is not clear what, if any, is the role of speed in the previously reported substantial age differences in logical problem solving. It is expected that present work will make further contributions toward the delineation of the mechanisms of aging in the central nervous system and behavior, particularly with regard to higher cognitive processes.

Nearing completion is a followup study of a group of men over the age of 65 who have been intensively studied from psychiatric, psychological, social, medical and physiological points of view. The report of the initial work is now in final draft by the collaborating investigators from the Laboratory of Clinical Science, Laboratory of Socioenvironmental Studies, and the Section on Aging. Findings show a relation of health to psychological functioning. However, certain changes such as those noted in the individual's mental capacities and social relations do not stand in a simple one-to-one relation with measured physiological changes. Analysis of the recently obtained longitudinal data will throw light on some of the supposed cause-and-effect relations in the mental and physical well-being of older persons.

EXTRAMURAL PROGRAMS

Research

A wide range of research activities in aging is carried out through the grant programs of the Institute. During fiscal year 1961, 41 research projects were being supported, totaling $1,373,000. It is estimated that $1,750,000 will be expended in 1962 and approximately $2 million in 1963.

Since relatively little is known of the sources of optimum mental and emotional functioning in the aging person, research must be conducted on a broad front. Some studies are concerned with the effects of aging on the central nervous system, cerebral physiology and other basic biological processes. Others deal directly with changing psychological capacities and functions. Still others are concerned with social processes which affect mental and emotional well-being in the later years.

Of special note are the studies in aging being conducted as part of the expanding NIMH international research grant program. One tripartite study will permit cross-national comparisons of important social aspects of aging in the United States, England, and Denmark. By using comparable sampling techniques in each country, investigators will be able to contrast aged persons in terms of, for example, their general level of physical functioning; services necessary to maintain the aged in their homes; sources of income; reasons for retirement; the role of the family in later life; and differences in life situations between persons over and under 75. In another study, a series of seminars has been initiated on cross-national research in human development, including patterns of aging; one of the goals here is to identify important areas for collaborative cross-cultural research.

Mental health project grants are supporting several applied studies including therapeutic techniques for the emotionally and physically handicapped, use of community nursing facilities as an alternative to institutionalization in a State mental hospital, optimal housing developments and workshops for older unemployed persons.

Training

Nine training grants are currently active specifically relating to aging, a total of $175,167. These grants are primarily in psychiatry and psychology. The funds are used both for faculty salaries and for stipends. This development is relatively new but it is anticipated that it will soon produce needed specialists in aging in the field of mental health.

Technical assistance

The Community Services Branch has recently added a special consultant on aging and chronic diseases to the staff of its Special Program Development Section. Various staff members have been working with national and volunteer agencies and also assisted in planning and conducting the White House Conference on Aging. One major focus this past year has been on the type and quality of care in nursing homes in relation to the mental health needs of older people, many of whom are not overtly mentally ill but have a variety of mental or emotional deficits or handicaps. It is apparent from annual reports of the regional mental health consultants that a significant portion of their time is spent in consultation in this field. Although developments in the States are on the whole rather slow, occasionally they are rapid, dramatic, and hopeful. As an example, a comprehensive program for the care of the aging has developed in the Western Pennsylvania Mental Health Center near Harrisburg, including an evaluation clinic, day-care center, placement program, and the initiation of a 140-bed halfway house.

Biometrics

Basic data on hospitalization of the aged mentally ill was presented in last year's report. This revealed deceleration of the first admission rate to State mental hospitals among persons 65 and over, increased use of general hospitals for all types of psychiatric patients including the geriatric, and the extremely low release rates and high death rates for patients over 65 resident in State mental hospitals.

Data are not yet available by age for 1961. However, the number of patients in mental hospitals in the United States excluding Alaska and Hawaii (for statistical purposes) dropped from 535,445 to 526,414. This drop of about 9,000 contrasts with drops of about 3,000 in each of the past 3 years. It is believed that geriatric patients shared in this drop, possibly at a higher rate because there has been a marked acceleration of placement in nursing homes.

PROFESSIONAL SERVICES BRANCH

The Professional Services Branch is sponsoring three pilot and developmental studies through special grants. This research is focused both on the psychological and social processes of normal aging as found among noninstitutionalized populations, and on factors which lead to severe breakdown and hospitalization in a mental institution.

The staff of the University of Chicago's study of social and psychological aspects of successful aging has published "Growing Old," by Elaine Cumming and William Henry (Basic Books, 1961). Its main theme is the process of disengagement, or the tendency to drop the responsibilities and relationships of the middle years and to derive satisfaction from less practical activities—and for some, from self-realization and enjoyment. New perspectives are given to the widely held popular notions of loneliness and isolation of the aged. This book has already stimulated numerous discussions and research proposals and will undoubtedly serve as a focal point for continued research. This study itself is now in its final phase. Interviews have been completed with about five persons close to each of the original subjects themselves. A second volume is planned which will focus on further analysis of the disengagement hypothesis and analyses of personality in the later years of life satisfaction, and of styles of aging in relation to the viability of older people.

An extensive study of persons hospitalized for mental and emotional disorders, over the age of 60, and for comparative purposes of a similar age group living in the community, is underway at the Langley Porter Neuropsychiatric Institute in San Francisco. Data have been gathered on about 600 hospitalized patients and 600 subjects in the community. Two rounds of followup data have been gathered on each group. The richness of this unique body of data promises to throw much light on reasons for mental breakdowns among the elderly.

A study of personality and social adjustment of a group of working-class men, pre- and post-retirement, has been completed by the University of California's Institute of Industrial Relations. It sharply delineates types of personality and adjustment in relation to retirement and aging, from the characteristics of mature aging through a "rocking chair" type to more disturbed forms.

SUMMARY

In general terms, the Institute through its own research program and through its grant program is approaching the study of aging on three broad fronts: *a*) research on the pathological conditions associated with the aging process; *b*) research on the normal aging process; and *c*) research on the assets of the aged so that these may be more fully utilized in achieving and maintaining mental health. Scientific advances in each of these areas is required if the individual suffering and social costs associated with aging are to be reduced. Research in the disease processes associated with aging is essential for the development of techniques of intervention. The development of preventive measures is dependent upon knowledge gained regarding the factors associated with nonpathological aging. Finally, it is necessary to evaluate the assets which the aged possess if their full potential for healthy living is to be realized.

EPIDEMIOLOGY

Mr. FOGARTY. Also give us a statement on your epidemiology studies.

(The statement subsequently submitted follows:)

SPECIAL REPORT—EPIDEMIOLOGY

Epidemiological investigations of the mental disorders are carried out to discover associations that may lead to the determination of factors—biological, social, cultural, and environmental—which cause these disorders and which are responsible for the disabilities they produce. These associations are determined by studies of rates at which disease develops in various population groups and of the differential duration of disease and disability and of mortality in affected individuals. One major purpose of these studies is to provide facts about treated and untreated diseases in the community and to delineate population groups with high rates of disability that should be singled out for special attention in the planning of community mental health services. Such facts are needed for the intelligent administration and evaluation of psychiatric services and for the more effective use of the limited number of skilled mental health professionals. The second major purpose of epidemiological research is to uncover important variables to be considered in the search for causes of specific mental disorders and for methods for their prevention and control. Thus, such research may lead to the discovery of those features of the habits, organization or environmments of human populations which may affect the onset or course of mental disorders and provide a basis for assessment of their relative importance in the etiologic structure of these conditions.

Research on the epidemiology of mental disorders is carried out by the National Institute of Mental Health primarily through the activities of its Biometrics Branch and the Mental Health Study Center. In addition, research in the area of epidemiology is supported by the Institute through grants and contracts. The following is a summary of the activities of the Institute in this area.

BIOMETRICS BRANCH

Primary emphasis of the research program of the Biometrics Branch is on studies of factors related to the extent of disability resulting from mental disorders. The Branch carries out studies to determine the effect of various demographic, social, economic, and cultural factors on the patterns of usage of various psychiatric facilities and the duration of stay within such facilities. A brief description of the activities of the Branch related to epidemology follows:

Annual collection of psychiatric care data

Data are collected annually on patients coming under care in 285 public mental hospitals, 270 private mental hospitals, 592 psychiatric units in general hospitals, 1,506 outpatient psychiatric clinics, 113 public institutions for the mentally retarded, and 195 private institutions for the mentally retarded. These provide nationwide and State by State estimates of the rates at which patients come under psychiatric care, measures of the rate at which patients are released from these facilities, staffing patterns, and data on expenditures for the care of patients. These data are published annually and distributed widely to persons concerned with mental health programs and the operation of psychiatric facilities and to those engaged in epidemiologic and basic research.

Model reporting area for mental hospital statistics

To obtain more meaningful national data based on uniform definitions for the public mental hospitals, the Institute sponsors the Model Reporting Area for Mental Hospital Statistics. This group now consists of representation from 27 States whose mental hospitals account for 80 percent of the patients in public mental hospitals on any one day. Representatives of the member States have agreed upon uniform definitions of terms describing movement of patients through the mental hospitals and are working cooperatively with the Biometrics Branch in conducting studies on the rates of movement of patients through the mental hospitals and assessing the effect which various intra- and extra-hospital factors have upon the movement rates.

Outpatient psychiatric clinic reporting

Similar efforts are being made to standardize definitions and develop meaningful tabulations on patients coming under care in outpatient psychiatric clinics. Tabulations of patient data are now being received from States for 1961 based on a revised format consisting of (1) routine or annual reporting of certain basic data, plus (2) special or cyclical reporting of data on a selected topic such as adolescence or mental retardation. The 1961 special tables are concerned with patient characteristics (age, sex, color, mental status, diagnosis). This information will be related to the 1960 census for computation of appropriate rates. The States are now being queried to ascertain their special interests for 1962 tables.

Studies of patients coming under care in other types of facilities

Methodological exploration is under way in limited geographic areas to determine the extent to which psychiatric patients come under care in outpatient facilities other than psychiatric clinics. Alcoholic and mental retardation clinics under medical nonpsychiatric direction and psychological clinics have been suggested for early trial reporting. The Branch is conducting pilot investigations of family service agencies in developing an internal recordkeeping system to provide basic data comparable to that for clinics.

Monthly mental hospital population movement data

The States in the model reporting area have been contributing to a system of monthly reporting of total mental hospital population movement data. The Biometrics Branch prepares nationwide estimates of the number of resident patients at the end of the month, the total number of admissions, the number of net releases, the number of deaths and corresponding rates based on the appropriate populations. These estimates are based on data supplied by some 30 States. They are published each month in "Indicators," a publication of the Department of Health, Education, and Welfare to show the trend in hospital population movement over time. The data are used by State administrators to assess their own programs.

Socioeconomic studies

The Biometrics Branch is conducting a study, the primary objective of which is, to determine the extent to which various socioeconomic groups in the population utilize the different psychiatric facilities within a State. In order to attain this objective it is necessary to have basic socioeconomic data on the patient and members of his family which can be related to similar data obtained from the general population as enumerated in the 1960 U.S. census. This study is being carried out in two States, Maryland and Louisiana, where basic identifying information has been obtained for each patient admitted to the public and private mental hospitals, the outpatient psychiatric clinics, psychiatric services of general hospitals, and the inpatient and outpatient psychiatric facilities of the Veterans' Administration during the period July 1, 1960, to June 30, 1961. This information is now being transmitted to the Bureau of the Census where procedures are being carried out to locate the 1960 census schedules for these individuals. The Census Bureau will then tabulate detailed socioeconomic and family characteristics of these individuals and will prepare similar tabulations of the populations of these two States. This study will provide a large number of specific hypotheses to serve as a basis for a wide range of epidemiologic investigations over the next few years. Certain geographic areas will be singled out as being associated with high rates of admission to psychiatric facilities, and certain types of families will be identified as "high risk" families in terms of the extent to which they generate admissions to psychiatric facilities. The efforts of control programs can then be concentrated on these groups.

Followup study of psychiatric admissions to Charity Hospital, New Orleans, La.

Over the past few years there has been an increasing number of psychiatric admissions to general hospitals in the United States. To investigate the effect this trend is having on the number and characteristics of admissions to other psychiatric facilities, a study has been initiated in cooperation with the Louisiana State Department of Hospitals to determine what impact the psychiatric units of Charity Hospital, a large public-supported general hospital, in New Orleans, have on the other psychiatric facilities in the area served by the hospital. Data to be obtained on the group of patients admitted to the psychiatric units of Charity Hospital during the period June 1, 1960, to May 31, 1961, will provide the following kind of information: (1) The patient's experience during the year following admission with respect to admission to other psychiatric facilities and contacts with other agencies or facilities that serve the community, such as family service agencies, welfare agencies, nursing homes, homes for the aged, etc.; (2) the characteristics of patients released to other facilities from Charity Hospital as compared with the characteristics of patients released to the community; (3) the extent to which recommendations made to the patient at the time of release from Charity Hospital are subsequently carried out; and (4) the changes that may have occurred in the socioeconomic and family characteristics of a sample group of these patients during the year following admission.

Psychiatric case registers

Under a cooperative arrangement between the Maryland State Departments of Mental Hygiene and of Health, and the Biometrics Branch of the National Institute of Mental Health, a psychiatric case register for the State of Maryland was begun on July 1, 1961. Individual patient reports are being collected from the public and private mental hospitals, the psychiatric services of general hospitals, outpatient psychiatric clinics, and the inpatient and outpatient facilities of the Veterans' Administration. Under the register plan all the routine reports referring to the same individual will be linked by the register number to provide a record of his psychiatric experiences over long periods of time and involving different facilities. The register will provide minimum annual and long-term estimates of incidence and prevalence by various demographic and socioeconomic characteristics and aid in the study of the results of psychiatric care, the flow of patients from one therapeutic resource to another, the variations in diagnostic classification and in previously reported care, and the natural history of mental disorders. The branch has also provided detailed consultation to the State of Hawaii for the development of a similar register involving patients coming under care in the different types of psychiatric facilities. These registers will provide extremely valuable information, not only on the total unduplicated counts of individuals receiving psychiatric care, but in terms of assessing the interrelationships among the various types of psychiatric facilities.

Study of factors in the development of emotional disorder

The biometrics branch is conducting a controlled retrospective study at the Johns Hopkins University on factors in early life that may be associated with development of emotional problems in children. The study uses interviewing techniques and record search for data to test several hypothesis related to the role of various patterns of child-rearing practices, handling of aggression and parental deprivation in personality development. A number of studies have dealt with the area of early infantile socialization experiences. However, results have been equivocal and much of the methodology has been questionable. The present study investigates the experience of a patient sample and two matched control samples, one drawn from the school population and one from other clinics at Johns Hopkins. The questionnaire and interviewing protocol was developed and pretested by a member of the branch. In addition, the Parental Attitude Research Instrument is being used. Interviewing is now being conducted and pilot study results are expected to be completed by the end of 1962.

Studies on the outpatient clinic population in Maryland

Two special studies have been completed on the Maryland outpatient clinic population. Cohorts of both child and adult patients who were admitted during an 18-month period were classified by diagnosis and statistically followed using modified life table techniques. The length of clinic care, type, and amount of service, outcome after treatment, and disposition were analyzed in order to learn whether the psychiatric classification represents an operationally important variable in determining the course and outcome for clinic service in order to evaluate this modality of care for various diagnostic groups. The study on children showed a distinct dichotomy in the brain syndrome and nonorganic mental deficiency cases, on the one hand, and the psychogenic disorders on the other. The first diagnostic group is distinguished by the considerably briefer service patients received. Within the psychogenic disorders for children the specific rubrics are not clearly demarcated by outcome. Among adult patients, in contrast, the major rubrics are fairly distinctive in outcome; the specific disorders provide even further and more useful delineation. Alcoholism patients, for example, have considerably lower treatment and improvement rates than patients with other personality disorders.

Studies of hospitalization in Ohio

Based on data obtained from the Ohio Department of Mental Hygiene and Corrections the branch is conducting a study of the probabilities of discharge. death, or continuous retention on the books of the hospital for a 5-year period among first admissions to the State mental hospital system during the years 1948–52. In addition to diagnosis, age, sex, race, marital status, education, occupation, residence, and religion are taken into account. Papers presenting some of the findings of the study include analyses of the experience of the following diagnostic groups, mental diseases of the senium, alcoholic psychoses, and schizophrenia.

The data on first admissions to the Ohio State mental hospitals for the years 1948–52 served as a basis for a detailed study of the rates of first admission according to specific demographic characteristics of the population. Plans are now underway to obtain similar data for a period centered around the 1960 population census. This will make possible a comparison of first admission rates between the two periods for population groups defined by specific characteristics.

Effect of distance from the hospital on first admission rates

A study was conducted in cooperation with the Warren State Hospital, Warren, Pa., to assess the effect of distance from the hospital on first admission rates. Concentric rings were drawn around the hospital covering the 13-county area served by the hospital and rates of first admission to the hospital were computed for each ring. The rates were highest for the area immediately adjacent to the hospital and decreased progressively with increasing distance from the hospital. This gradation, however, was accounted for primarily by persons with mental diseases of the senium and those with psychoneuroses, while the rates for those with schizophrenia appeared to be independent of distance. These findings suggest that local facilities do not have the trained psychiatric personnel, the therapeutic services or the necessary physical facilities to cope with the special behavior problems presented by schizophrenics. On the other hand, the behavior and physical problems presented by patients with mental disorders of the senium are such that facilities such as general hospitals, nursing homes, and homes for the aged, or home care may be used more extensively as alternatives to the mental hospital for these types of cases in areas more remote from the mental hospital.

International studies

Studies have also been carried out of comparisons of diagnostic differences in first admission rates to the mental hospitals of the United States and those of England and Wales. Some extraordinary differences have been revealed between the first admission rates for manic depressive and cerebral arteriosclerotic psychoses. The manic depressive psychoses rates to mental hospitals in England and Wales is 18 times the rate to the public hospitals in the United States and 9 times the rate of first admissions to both the public and private hospitals. With respect to the rate for psychoses with cerebral arteriosclerosis, the ratio of the total first admission rate to the public hospitals in the United States to the rate for England and Wales is 6 to 1 and if the rates for the public and private hospitals are used, the corresponding ratio is almost 7 to 1. At this time it cannot be determined how much of these differences are attributable to differences in the diagnostic criteria and diagnostic nomenclature used by the English and American psychiatrists to characterize patients who may present the same clinical picture at time of admission or to actual differences in the distribution in specific types of patients admitted to the mental hospitals in each of the two countries. Plans are underway to develop studies that will begin to make possible explanations of differences such as those discovered.

Classification of mental disorders

Another activity of the biometrics branch relates to the work attendant to the revision of the section of the International Statistical Classification of Injuries, Diseases, and Causes of Death that pertains to the mental disorders. The chief of the branch works very closely with the chairman of the U.S. National Subcommittee on revision of the classification of mental disorders and the American Psychiatric Association Committee on Nomenclature and Statistics to develop U.S. recommendations for revision of this classification. In addition he is a member of the Subcommittee on Classification of the Expert Committee on Health Statistics that is dealing with this problem on an international level.

Collaboration with the World Health Organization

The biometrics branch has collaborated closely with the Mental Health Unit of the WHO in relation to the latter's international program in the epidemiology of mental disorders and the development of basic statistics on the care, treatment, and rehabilitation of the mentally ill throughout the world. The chief of the branch has served as a consultant to the WHO for the purpose of providing guidance to both its Mental Health Unit and to the Governments of Australia, Philippines, Taiwan, Japan, and Israel in the development of their national programs in this field.

MENTAL HEALTH STUDY CENTER

A primary focus of program activities at the Mental Health Study Center is to further develop a community based research facility utilizing epidemiological or sociopsychological methods to describe characteristics of various population groups along a continuum of mental health to mental illness. The operation of clinical services providing diagnosis and treatment to county residents, consultative services to community agencies, caretakers, and the participation in community planning provides a sound basis for conducting specific collaborative studies. A number of specific studies now underway represent part of an effort to develop a complete reporting system from community agencies on mental health problems.

SPECIFIC STUDIES

Reading ability and outcome

This project was initiated in 1954 as a cohort study of the entire sixth grade in Prince Georges County school system in that year. The cumulative records of over 3,500 students in the sixth grade at that time have been made available for each successive year to the staff of the study center. This makes it possible to analyze the possible relationship of reading performance to other variables such as intelligence, sex, ordinal position, etc. At the present time coding and checking of missing data is in process and it is anticipated that the analysis of the sixth grade data will be completed by January 1963.

The study of children who absent themselves from home

Five agencies, juvenile court, juvenile squad, county probation and parole department, pupil personnel services of the board of education, and the Mental Health Study Center are engaged in developing a comprehensive reporting system for children who are reported to law enforcement authorities as absent from home. It is anticipated that this study will throw light on the antecedents of this behavior and possible methods for improving the management of these children. The study also serves as a pilot method for the operation of a community reporting system and for specifying principles of collaborative studies with county agencies.

Study of clinic contacts from community resources

During the past year the staff has been involved in an investigation of the consultation and referral requests made by community professionals during the past 10 years. The study is designed to investigate trends and referral patterns, to relate characteristics of mental health problems referred to the community resources, and to compare selective characteristics of cases accepted for treatment or for evaluation with those not accepted. The source of the data for this study is the center's clinical consultation record form. From this study it is anticipated that valuable leads may develop, revealing possible trends over the 10-year period.

Three other studies aimed at understanding either the characteristics of the clinic population or those of professional individuals referring patients to the clinic may be briefly cited. One study reviewed systematically the most visible characteristics of some 60 families seen in family group therapy at the study center. This study revealed that those families who became involved in family group therapy have a tendency to come to the center because of an eldest child who is in junior high school, who is doing poorly academically, disrupts the classroom, perhaps shows destructive behavior in the community, and who is at open warfare with his parents at home. Another study of the characteristics of families given service during a year's time revealed among other findings that one out of three of the families had both parents working and that in half of the parents there was a difference in educational level between parents. A third study related to our clinical services was an analysis of cases referred by county physicians over a 5-year period. Data utilized in the study included age, sex, marital status, index of social position, size of household, total number of interviews, benefit from clinical contact, etc. Some of the findings include the fact that physicians tend to refer a high percentage of cases diagnosed as psychoneurotic and tend to refer the adult female to the clinic whereas the young male is more likely to reach the clinic by way of referral from the school system.

A public health approach to the problems of alcoholism

This project conducted in the setting of the local Prince Georges County Health Department and funded through the National Institute of Mental Health has as one of its goals the gathering of incidence and prevalence data on alcoholism in Prince Georges County. At the present time, one 6-month research pilot project is being completed studying three categories of patients, namely these: (1) Discharged from Spring Grove State Hosiptal to Prince Georges County; (2) Prince Georges County Hospital patients referred to the alcoholic clinic, and (3) those patients who have been inactive in the clinic for at least 6 months.

The observation has been made that a high percentage of patients from the Prince Georges General Hospital where a clinic psychiatrist is in attendance are able to accept treatment at the clinic. This procedure has resulted in the assignment of a mental health nurse to Spring Grove State Hospital to facilitate this referral process. This type of referral and clinic procedure which utilizes other staff members in the health department, particularly the public health nurses, is expected to provide data concerning treated prevalence for those suffering from different degrees of alcoholism in the county.

RESEARCH GRANTS

During 1961, 13 grants, totaling $341,666, were awarded by the National Institute of Mental Health for research related to the epidemiology of mental disorders. These grants supported investigations in alcoholism, suicide, ethnic, and migration factors in the development of mental illness, community and hospital factors associated with the care and treatment of the mentally retarded, patterns of medical care related to mental illness, statistical followup of released mental patients, cross-cultural study of psychopathology, sociological problems in human genetics, studies of differential rates of schizophrenic and endemic hysterical reactions, and a study of the role of a local health unit in mental health.

SPECIAL CONTRACT

On June 15, 1961, the National Institute of Mental Health negotiated a contract with Harvard University School of Public Health to prepare a document or documents concerning what is known about the cultural epidemiology of diseases, with emphasis on chronic diseases and due attention to problems of mental illness. This work is proceeding upon schedule and the diseases which will be carefully studied are rheumatoid arthritis, schizophrenia, and hypertension.

It is planned to hold a conference of a small number of people later this calendar year to which distinguished social scientists, medical scholars, and epidemiologists will be invited to assess the report submitted by the Harvard School of Public Health and to make recommendations with respect to the most effective ways of increasing the knowledge in this area and of utilizing it for the control and prevention of diseases.

MINNESOTA MULTIPHASIC PERSONALITY INVENTORY

Mr. FOGARTY. What is the Minnesota Multiphasic Personality Inventory?

Dr. FELIX. The MMPI—Minnesota Multiphasic Personality Inventory, was developed by Drs. Hathaway and McKinley, professors on the faculty at the University of Minnesota. This is an instrument which is a very sensitive one in terms of detecting nuances in the personality.

It consists simply of a whole series of cards which have certain statements on them as to what a person thinks or feels about a whole variety of things. They sort these into three boxes: One, they agree; another one, if they don't agree; and another one, they don't know.

On the basis of thousands of cases which have been analyzed, they have developed what they call a profile. If you get a certain score among these, you can pretty well predict a variety of different kinds of personality makeup.

This is being used experimentally in a number of places. One large clinic in the country, I understand, is going to come to us soon for a grant to carry on a most interesting study. They have MMPI's now on several thousand patients who have been admitted with all kinds of things—ulcers, arthritis, heart disease, tuberculosis, cancer, every sort of thing. All have had the MMPI. They now wish to run these through a computer to see if they can get any kind of hint as to whether certain types of personalities may be more predisposed towards certain types of illnesses than others.

This clinic is not a psychiatric clinic. Off the record.

(Discussion off the record.)

Dr. Felix. This clinic is a distinguished general medical clinic, and this is a project in which men from the Departments of Medicine and Surgery, as well as Psychiatry and I think some other departments, are equally interested.

This is an example of how this particular tool is used.

MENTAL HEALTH PROJECT GRANTS

Mr. Fogarty. Doctor, will you supply for the record also a statement on your mental health project grants under Title V.

Dr. Felix. Yes, sir.

(The requested information follows:)

Special Report: Mental Health Project Grants

The Mental Health Project Grants program was established by the Health Amendments Act of 1956, title V, and the first grants in this program were made in the fiscal year of 1958. As of December 31, 1961, a total of 321 grants had been made.

The Mental Health Project Grants program was initiated as a response to a long-standing recognition of the need to develop improved methods of diagnosis, care, treatment, and rehabilitation of the mentally ill. The grants are made to governmental and private State and local agencies and institutions, hospitals, research facilities, educational institutions, and individuals.

Projects may take the form of demonstrations, pilot projects, surveys, conferences, administrative research, and experimental studies. They include studies of: new methods and concepts of treating patients; methods of prevention and early detection of mental illness; effective and economic alternatives to hospitalization; rehabilitation and reintegration of discharged patients into the life of the community; public education in mental health; ways to better utilize existing community mental health agencies; ways to improve administrative practices in mental institutions, and the role of private psychiatric personnel and facilities.

ALCOHOLISM

The problem of alcoholism affects a large number of persons and is a major cause of many economic, social, health, welfare, and family problems. Dealing with the problems of alcoholism is complicated and difficult because of the reluctance of the alcoholic to seek and accept treatment, and because many community treatment resources—general practitioners, outpatient psychiatric clinics, and general hospitals—do not provide appropriate services to the alcoholic. To help overcome these difficulties, 11 Mental Health Project Grants relating to alcoholism have been made. They include the following:

A project at the Massachusetts General Hospital in Boston is studying the feasibility and effectiveness of a treatment and rehabilitation program which begins in the hospital emergency ward. Preliminary reports show that persons admitted with a diagnosis of alcoholism who receive special care and attention in the emergency ward are more likely to continue treatment than those receiving routine medical care.

The Nebraska Psychiatric Institute conducted a training course for physicians designed to improve the effectiveness of the general practitioner's treatment of alcoholics.

The National Council of Alcoholism has a project focused on exploring variables concerned with socio-economic background and marital roles as they relate to family adjustment problems associated with alcoholism; it is also studying the prevalence of alcoholism in an urban community.

The Mississippi State Department of Education received a developmental grant to assist them in planning a comprehensive community alcoholism education program.

JUVENILE DELINQUENCY

In 1961, the number of grants relating to delinquency and criminality made under the Mental Health Project Grants program was more than double the total number of grants made in this field in previous years. In all, 40 grants have been made in these areas. Many of these center around: (1) the need for an adequate definition and delineation of problem areas in delinquency; (2) the need for effective prevention and treatment methods; and (3) the need for training both professional and nonprofessional workers in this area.

Among the project grants focusing on an adequate definition and delineation of problem areas are the following:

In Wisconsin, a study designed to identify the varying characteristics of young people who exhibit socially approved and nonapproved behavior has been undertaken. A unique aspect of this study is the fact that rural as well as urban boys and girls are being studied. Results of this study will be compared with results of similar studies conducted in cities.

The National Council on Crime and Delinquency has a grant to establish a clearing house for information in this field. In addition, the grant will enable the National Council to review, analyze, and evaluate findings and developments in the field, to stimulate and increase the quality and quantity of research and experimentation being conducted, and to undertake special studies and reviews.

Among the project grants focusing on the need for effective methods of prevention and treatment are the following:

In New York City, a project has been designed based on the theory which hypothesizes that the development of delinquent subcultures is a result of the lack of integration between the cultural and social structures of the community. This theory postulates that the alternative forms of opportunity offered by the community to its young people account for the particular form and content of delinquent subcultures. The project will develop detailed plans for intervening directly in the cultural and social processes in the community that are identified as producing the delinquent subcultures.

In Connecticut, a project designed to demonstrate the effectiveness of providing a psychiatric and rehabilitation service to young inmates in county jails was conducted by an interdisciplinary team.

Several project grants focusing on the need for training professional and nonprofessional workers in the field of juvenile delinquency are described in the section summarizing grants relating to manpower needs. The various types of personnel who have received such specialized training include judges, police officers, and social workers.

MANPOWER

One of the major problems to be overcome if the mentally ill are to be given proper care and treatment is the acute shortage of professional and other trained personnel available for work in this field. Seventy-one project grants have been made that relate to meeting the needs of various types of personnel for training in psychiatric techniques and in mental health problem areas. The scope and importance of these projects is illustrated by the brief descriptions that follow:

Two grants that enable personnel working in mental hospitals, in clinics, and on State mental health commissions to visit and observe what is being done in institutions other than their own have been made to the southern regional education board.

The importance of the proper training and utilization of the psychiatric aide has been recognized through grants made to Topeka State Hospital and Osawatomie State Hospital and the National League for Nursing. The later grant was made for a project demonstrating the usefulness of a clinically centered seminar in improving the skills of the nurses supervising and instructing psychiatric aides.

The Western Interstate Commission for Higher Education has a grant designed to increase the professional skills of psychiatric nursing directors, and another grant designed to promote a staff development program for personnel serving in schools and hospitals for the mentally retarded.

The importance of the work done by volunteers serving in various psychiatric institutions and mental health programs has been recognized in several project grants. One such grant, to the National Association for Mental Health, was made for an institute for mental hospital directors of volunteers. The proceedings and findings of this institute have been published. A project evaluating the work of student volunteers in the Boston area is underway, and a project demonstrating how student volunteers might work with disturbed children is being conducted in Vermont.

To develop more and better qualified personnel for work in the area of juvenile delinquency, grants have been made to the University of Minnesota and to the National Council of Juvenile Court Judges for conducting institutes for juvenile court judges. Material to be used in training police for juvenile delinquency work is being prepared through a grant made to the Public Affairs Committee. Among the other grants for training made in this area is a small grant made to the Nevada State Prison for the in-service training of prison officers.

Other training needs have been recognized in grants made to improve the administrative skills of commissioners of mental health and mental hospital superintendents, to train clergymen in the principles and techniques of pastoral counseling, and to train personnel in the special problems of working with the mentally retarded, and with the emotionally disturbed child.

MENTAL RETARDATION

Twenty projects to study and demonstrate various approaches to the problems of mental retardation have been made under the project grants program. Some of these projects are briefly described below.

At the University of Nebraska College of Medicine a preadmission, receiving, diagnostic, and treatment center for children under 6 was established on the medical school campus. Reports indicate that this project has demonstrated: (1) that a significant number of retarded children can be cared for without institutionalization; (2) that interdisciplinary clinical investigations are necessary to establish a correct diagnosis; (3) that treatment in many cases can be carried out on either an outpatient or an inpatient basis; (4) that several organic and emotional factors may contribute to the misdiagnosis of mental retardation. In Iowa, the Des Moines Child Guidance Center has established a day hospital providing diagnostic and treatment services for children having severe mental disorders.

The problems of data collecting and record keeping in the field of mental retardation are being investigated at Pacific State Hospital in California and at the Jewish Hospital in Brooklyn, N.Y. The medical data processing laboratory being established at Pacific State Hospital will eventually, it is hoped, develop techniques to identify, define, and quantify the significant variables relative to the prevention, diagnosis, and treatment of the mentally retarded. The project at the Jewish hospital will involve analyzing case record data collected on several hundred cases seen in a community retardation clinic, and developing a comprehensive method for recording and analyzing these data.

The problems of young children with communication disorders, some of whom are mentally retarded, are being investigated at St. Joseph's School for the Deaf in New York City, and the University of Kansas has a grant to develop a first-rate language and communication program for mentally retarded children.

The feasibility and usefulness of providing community-centered services and facilities for the mentally retarded is being investigated and demonstrated through a number of project grants. In New York City, grant funds are enabling the Shield of David to establish a group and home training program for 3- and 4-year old retarded children. Also in New York City, the Association for the Help of Retarded Children has established a day program to train mentally retarded young adults in the elementary skills necessary to daily living, and to give counseling to parents; the goal of this program is to enable the retarded person to live at home rather than in an institution. The effectiveness of a combined workshop and activity program as an alternative to institutionalization is being demonstrated in a project developed by the United Association for Retarded Children in Milwaukee.

Several grants are focused on the need for developing trained personnel to work with the mentally retarded. Thus, in New Jersey, support has been given for a project developing a training program for attendants serving in institutions for the mentally retarded; in Kansas, a small grant has enabled social workers to visit institutions for the mentally retarded in other States, to assist them in developing improved social work methods and practices in their home institutions; in New York City, a project has demonstrated how the public health nurse can provide home visiting and consultation services to retarded children and their families.

Other grants made in the field of mental retardation have provided for the consultation needed to design a special treatment program for retarded delinquent boys in North Carolina, and to plan a program of education and research at the Lynchburg Training School and Hospital in Virginia. In Massachusetts, a grant was awarded to support a Governor's conference on mental retardation that sought to develop greater coordination among the various agencies concerned with services for the mentally retarded.

NARCOTICS ADDICTION

A grant was made recently to establish a narcotics addiction service center in Connecticut. The center, a demonstration project, would provide for the diagnosis and evaluation of cases, for referral services to appropriate health and social agencies, and for consultation services to agencies.

SCHOOL MENTAL HEALTH

The magnitude of the school population and the need to do whatever is possible to develop the mental health of the Nation's children have made the study of mental health in schools a prime responsibility. Thirty-four grants related to school mental health have been made through the mental health project grants program. In 1961, the number of grants made in this field was twice as large as those made in 1960. Subjects being studied include techniques for the early detection and management of emotional illness, the effectiveness of added school services in relation to maladaptive behavior, and mental health education programs for mothers of schoolchildren. Some studies directly related to program planning to meet special needs concern the following: The rehabilitation of emotionally disturbed blind children, a language program for mentally retarded children, and a pilot day nursery for schizophrenic children. Other studies focus on interagency relationships such as those of clinics and schools.

More specific examples of the type of projects and studies being undertaken through the project grants program follow.

The preschool child and his family is receiving attention through a grant made in Boston, for work with multiproblem families with preschool children, and in Philadelphia, for a preventive mental health program for the preschool child and his family.

Training projects in Baltimore and Washington, D.C. are designed to train professional personnel for work with the emotionally disturbed preschool child, and to train school personnel for work with disturbed schoolage children.

Projects designed to minimize the effects of cultural deprivation in school children are being carried out in Illinois, where there is a project focused on the prevention of school problems and delinquency in children coming from lower-class neighborhoods, and in Tennessee, where there is a project designed to improve the intellectual functioning and personality adjustment of culturally deprived children.

In New York City, the effects of coordinated psychiatric and casework approaches in the treatment of the problems of primary school children is being investigated and an integrated school-clinic group treatment program, for adolescents with problems and their parents, has been established.

The George Peabody College for Teachers in Tennessee is developing a project designed to demonstrate how residential schools may be used for the reeducation of emotionally disturbed children. This project includes a specialized training program for teachers working with emotionally disturbed children, and a program of research and consultation. The project also aims to demonstrate that a residential school for emotionally disturbed children can be effective as an alternative to hospitalization, and as a post-hospitalization facility.

Several projects are concerned with the special educational needs for the mentally retarded and other handicapped children, and the mental health problems of college students are being investigated at Duke University, the University of Florida, and St. Francis College.

SUICIDE

A comprehensive suicide prevention program, in California, has been made possible by support from the mental health project grants program. The program includes a clinical center, which has the primary goal of saving lives by referral and treatment procedures, a research unit to study data obtained from the clinical service and to formulate and test hypotheses related to suicide, and a training center for the sharing and dissemination of the clinical skills and research findings developed by the clinical and research units. The project has proved to be a successful demonstration that such a suicide prevention program can save lives. It has also served as a pilot project and model for other communities planning such programs.

REHABILITATION AND AFTERCARE

The proper care and treatment of hospitalized mental patients necessitates the development of a comprehensive program of services that include not only care and treatment within the hospital proper, but preadmission services, and services designed to prepare the patient for his release from the hospital and for whatever post-hospitalization services he may need. The mental health project grants program is supporting about 60 projects demonstrating many different approaches to the aftercare and rehabilitation needs of mental hospital patients. These include occupational and social rehabilitation services and programs, the efficacy of various alternatives to hospitalization, aftercare services involving the use of the general practitioner and the public health nurse, and programs and projects that involve a good deal of hospital-community interaction. Some of these projects are described briefly as follows:

A project designed to explore how many different social agenices may cooperate in providing needed services to former hospitalized patients is underway in Connecticut. Under a grant given to the Community Council of Greater New Haven, family casework services, public health nursing services, and vocational counseling services are being made available to discharged patients. In Montana, a project is demonstrating how community provided social services may facilitate the release of hospitalized patients and provide aftercare in the community. In Idaho, a social service project attached to a State mental hospital is devoted to the problems of providing foster home care for mental patients.

Projects have been undertaken in Ohio, Maryland, Montana, Colorado, the District of Columbia, Michigan, Mississippi and in other States to study, demonstrate and evaluate the use of public health nurses in psychiatric aftercare services. How general practitioners may provide appropriate psychiatric treatment services to formerly hospitalized patients has been demonstrated in Nebraska and Vermont, where general practitioners have received special training in the needs of discharged patients, and where consultation services have been made available to them.

In any treatment program for the mentally ill, the role of the family in the life of the mental patient, and how the family adjusts to the patient's illness, is of major importance. In Illinois, a demonstration project has focused on the possibility of developing an informed and effective group of volunteer workers. These workers would undertake to assist patients' families to cope with the practical problems that result from having a family member hospitalized, and with the readjustments needed when the patient returns from the hospital. In California, New York and North Carolina, grants have been made to explore the possibilities of the use of family therapy in the treatment of schizophrenia. Several other projects have been exploring and demonstrating various techniques that may be used to involve the family, in a constructive manner, in the treatment, care, and rehabilitation process.

Attempts are being made to meet the occupational rehabilitation needs of mentally ill persons in demonstration projects being conducted in New York, Illinois, Massachusetts, and other States.

In general, the mental health project grants program is interested in supporting additional demonstration projects that involve new approaches to the care, treatment, and rehabilitation of the mentally ill. Some of these new approaches involve such "new" types of facilities as the day hospital and the night hospital, or such "new" uses of more traditional facilities, such as the use of specialized outpatient clinics—clinics meeting during the evening hours or in industrial settings. Other approaches that have proved to be effective in meeting the needs of formerly hospitalized patients involve the use of halfway houses, rehabilitation workshops, social therapeutic clubs, and pastoral counseling services.

SUICIDE

Mr. FOGARTY. And one on your activities with regard to suicide.

Dr. FELIX. Yes, sir.

(The requested information follows:)

SPECIAL REPORT: SUICIDE

INTRODUCTION

Suicide in the United States is a serious problem. It is the 11th leading cause of death; and for men, it is 7th. The aged and depressed individuals are exposed to the greatest risk, although suicide can and does occur among other segments of the population. The magnitude of the problem is increased when consideration is given not only to those who actually commit suicide but also to the more prevalent attempted suicides. Because of the inaccurate reporting of both actual and attempted suicides, no precise statements as to their incidence is possible.

The National Institute of Mental Health has been concerned with the problem of suicide and has for several years supported through its granting mechanism several studies in the area. For example, one study was related to the analysis of rescue fantasies of attempted suicides. The ultimate purpose of these studies was to provide some clues for early intervention.

PROGRAM DEVELOPMENT

While support for individual studies has been provided in the past, it is only within the past year that a systematic appraisal of the current state of knowledge and research needs of the field has been undertaken. As a result of this effort two grants of major importance have been made:

Review of current work on suicide.—This grant is under the direction of the eminent statistician, Dr. Louis I. Dublin. Its purpose is to organize and evaluate current knowledge and research concerning suicide and suicidal behavior. The emphasis is placed upon epidemiological, demographic, social, and psychological suicide data for the United States and other countries. This study should be completed within a year and will thus, provide an excellent point of departure for additional work in the suicide field.

A comprehensive suicide prevention program.—This is a major 7-year grant under the direction of Drs. Shneidmann and Farberow and is located in Los Angeles, Calif. While it is currently a demonstration project, originally it was a regular research grant. The present grant has three major functions. The first is to expand the operations of the Suicide Prevention Center which has close ties with other community agencies, e.g., hospitals, county medical association, ministerial associations, coroner's office, law enforcement officials, etc., and which serves to make appropriate referrals or to provide the necessary treatment. The second function is to provide training for other professional personnel who have an interest in suicidal behavior. In this regard, other cities, such as Indianapolis, Tulsa, Phoenix, Chicago, and New Orleans, are looking to the Suicide Prevention Center for guidance. The final function—research—is especially important. Because of the nature of its activities, the Center is gaining access to data which would otherwise not be readily available. Along with many journal articles, two major books have been produced by the Suicide Prevention Center: (1) Clues to Suicide, (2) The Cry for Help.

OTHER ACTIVITIES

While these two grants—one providing a review of current knowledge and the other developing intervention and prevention techniques—will serve as a basis for further work in the field of suicide, staff members have been engaged in additional activities. A special exhibit designed to call attention to research and control work being done on suicide prevention was prepared for scientific and professional groups. In addition, a brochure on suicide has been prepared and distributed. Work has also been started on the development and filming of a police training film on handling the depressed suicidal patient. In addition, plans are under way to make use of the 1960 census data for a study of the relationship between morbidity and mental illness, one facet of which will be suicide.

OVERVIEW

The Institute's program is designed to overcome some of the difficulties in developing effective prevention and intervention procedures in the problem area of suicide and suicidal behavior. The difficulties include inaccurate reporting of actual and attempted suicides, thus leading to uncertainty as to the magnitude of the problem. Also included is the difficulty of attracting competent investigators to the field—suicide, even among professionals, is a taboo area with social stigma attached to it. However, it is an important mental health problem and one in which the Institute is planning a systematic effort to reduce.

CLINICAL RESEARCH CENTER PROGRAM

Mr. Fogarty. Also place a statement in the record on your clinical research center program.

(The requested statement follows:)

Special Report: Clinical Research Center Program

RESEARCH CENTER AND PROGRAM-PROJECT GRANT PROGRAM

Development

The National Institutes of Health Clinical Research Center program was initiated during 1960 by awarding grants to establish multicategorical centers for general clinical studies. For 1961, Congress made funds available to expand this program in scope and concept. The new funds permitted not only the support of additional centers of the kind aided during the preceding year, but also the establishment of categorical centers for clinical research focused on a specific disease or group of related diseases. Under this expanded program, the amount of $500,000 was made available to the National Institute of Mental Health out of 1961 funds for the establishment and support of clinical research centers in the area of mental health. Accordingly, in November 1960, an information statement was published and distributed inviting interested groups to apply to the National Institutes of Health for mental health clinical research center grants.

The November announcement defined a clinical research center as a distinct organizational and physical entity providing a continuing framework for a clinical research effort, including the necessary laboratory, clinical, and supporting services. It indicated that the research may be directed either toward a large range of medical problems or toward a specific disease or group of related diseases and that the objective of such a center is to provide a stable organizational framework, an atmosphere of common purpose, and an intellectual and scientific environment for the integration and concentration of effort focused on clinical investigations. These studies, it was felt, would typically involve exacting observation of patients utilizing physiologic, metabolic, psychiatric, and other techniques. Also, it was expected that such centers might provide additional training opportunities and support appropriate teaching activities. The announcement further indicated that the center should be a discreet clinical unit including a research ward or wards in or attached to a hospital, a stable well-trained nursing and technical staff to provide precise control and observation of patients, and supporting specialized laboratory facilities. The program would provide support for any necessary alterations and renovations (exclusive of new construction) needed to provide for the necessary patient care and research space. In addition, it provided for the payment of hospitalization costs of research patients. The general model envisaged for these centers was typified by the metabolic units which were being established under the aegis of the Division of General Medical Sciences of the National Institutes of Health.

The development of the clinical research center program within the National Institutes of Health was extremely rapid, and its implementation—the establishment of policies and procedures, of minimum requirements, the preparation of and issuance of appropriate application forms, instructions, and announcements—all took place under considerable time pressure. Thus, although the November 1960 program announcement outlined certain formal requirements and procedures, there was general agreement that the concept of the program indicated therein was preliminary, and that modifications growing out of the first year's experience, would be very likely to occur.

In order to give fuller consideration to the special concerns of the National Institute of Mental Health in the new program, as well as to review the first group of applications which were submitted in response to the November announcement, the National Advisory Mental Health Council held a special meeting in April 1961. It was the consensus of the Council that while the model for a clinical research center which was proposed in the November announcement had considerable merit, it would not be desirable to restrict support under this program only to applicants who adhered closely to this particular model. It was suggested, for example, that the model of a metabolic facility might not be totally appropriate for the mental health field in view of the present state of the art in psychiatric research. The selection of this particular model for a clinical research facility to the neglect of other possibilities was deemed inadvisable. With this in mind, the Council recommended that the funds available for this program should be utilized to provide long-term programmatic support for a broad range of research approaches. Such an expanded program could provide for the support of centers designed to investigate basic behavioral processes, such as cognition, perception and communication, as well as for centers focusing on specific problems such as aging, mental retardation, juvenile delinquency, or schizophrenia. It was suggested that such centers might be based in academic institutions, in community organizations or in State hospitals and it was generally agreed that a variety of possible center formats would appear spontaneously. The Council saw no need to establish arbitrary limits on the development of such centers at that time.

The National Advisory Mental Health Council agreed on four major characteristics which were deemed to be critical in determining whether a given request warranted support:

(1) The presence of a central person with proven investigative or administrative competence who could gather about him a competent team of researchers at both a senior and junior level.

(2) A reasonable focus or concentration of concepts or approaches, as opposed to a shotgun expedition or broad, total institutional support.

(3) The above programmatic concentration should be on a broad, interdisciplinary basis.

(4) An opportunity should be provided for the effective research training of promising young investigators. (It was pointed out that this training function at present can best be carried out in a university-based or university-affiliated program.)

Following this and other discussions within the National Institutes of Health, a new policy statement was issued on June 26, 1961. The major change in this statement was provision for a much broader program of activities than the earlier announcement had included. In this new announcement, a clinical research center was defined much as it had been in the original announcement and the concept that a center grant was awarded solely "for the support of physical resources" was reinforced. In addition, however, a new type of grant, the program-project grant was announced. A program-project grant was defined as "a grant made to an institution, in the name of one or more principal investigators, for the support of a broadly based and usually long-term program of research activities. Program projects are flexible in nature, may require relatively large sums of money, typically involve the organized efforts of large groups, and may provide support for the basic physical resources. They are usually directed toward a range of problems within a broad category having central research focus rather than a specific single purpose." Thus, a center grant was restricted to pure facility support—alterations, laboratories, patient-care facilities and personnel to support these operations—while the new program project made it possible to provide support for the broad gauged research activities anticipated for a center, as well as, if necessary, for the facility itself. Funds earmarked for clinical research centers would, therefore, be applied to those awards which were made only for such centers, or for the "center" portion of a program-project grant.

Review procedures

As policies and procedures with regard to this new type of broad support developed, so also did the procedures for reviewing applications. Initially, in order to establish a viable program as quickly as possible, the review of applications was undertaken by an ad hoc committee within the National Institute of Mental Health. This review function was effectively carried on by a group of well-qualified outside consultants who gave generously of their knowledge and time to the Institute. However, as soon as the administrative arrangements could be made, a new Special Programs Review Branch was established in the Division of Research Grants with the responsibility for the initial technical review of program-project and clinical research center applications. Within this Branch the Mental Health Program-Project Committee was assigned the specific responsibility for applications assigned to the NIMH. The Mental Health Program-Project Committee began to function in the fall of 1961 and its first reviews were completed in time to be presented to the National Advisory Mental Health Council at its meeting in November 1961.

Activities

Inasmuch as the official announcement describing the clinical research center program was not released until November 1960, the first awards could not be made until late in 1961. In that year, a total of 15 applications requesting approximately $4,200,000 were received and reviewed. Three of these applications were recommended for approval by the National Advisory Mental Health Council. They carried awards of approximately $500,000 in center funds and $288,000 in research program-project funds. In addition, an award of approximately $246,000 for the support of a communications center in Massachusetts was made. This grant falls into the program-project category according to the revised guideline, but had originally been awarded before these were established.

As has been indicated, $500,000 was made available and expended for the center program in 1961. For 1962, $3 million was originally allocated for the clinical research center program, but this amount was reduced to $1 million as a result of the President's request to limit expenditures. As of the end of the second quarter of 1962, nine additional applications requesting a total of approximately $3,100,000 have been received and reviewed. Four of these were recommended for approval and paid, including one for the support of a center for alcohol studies, which had no clinical center component. Thus, for 1962, the total of $1 million allocated has already been obligated for the support of six clinical research centers (three new and three renewal grants), and $398,000 for research program-project grant support related to these centers. In addition, approximately $531,000 has been obligated for research program-projects which do not involve funds for clinical facilities. Of this latter amount, $178,000 is for the support of basic facilities and services, and $351,000 for research program costs.

Since the clinical research center program is new, involves large amounts of money and requires relatively complex planning, potential applicants have needed time to draft effective plans. Although some institutions were in a position to submit applications relatively quickly after the issuance of the program announcements, others are only now reaching the point where they feel they will be in a position to submit appropriate applications.

Preliminary expressions of interest in the program from at least 15 sources are on file as of the end of 1961, and there is every reason to expect that applications from many, if not all of these organizations, will be submitted for review during the forthcoming months. As the program becomes established and its guidelines better known, it seems likely that a higher proportion of the applications that are submitted will be recommended for approval.

Finally, it is noteworthy that in these initial phases of the clinical center program, although no particular attempt was made to seek diversity, either in subject matter or in the geographic location of approved programs, such diversity has developed naturally. Thus, the grants approved up to now are providing support for centers concerned with problems of adult psychiatry, early childhood schizophrenia, mental retardation, psychosomatic problems and alcoholism, and these centers are distributed in seven States: Illinois, Indiana, Maryland, Massachusetts, Nebraska, New Jersey and New York.

ROCKEFELLER PUBLIC SERVICE AWARD TO DR. FELIX

Mr. Fogarty. I think I had better stop and let someone else ask some questions.

First, I had just one other thing I wanted to mention. You were very kind to me a little earlier, Doctor; so I think we ought to put this in the record.

On November 17 the Director of the National Institute of Mental Health, Dr. Felix, was awarded the 1961 Rockefeller Public Service Award for contributions to science. The notification was:

> Dr. Robert H. Felix, Director of the National Institute of Mental Health, has been selected to receive one of the five 1961 Rockefeller Public Service Awards for his distinguished contributions to the field of science.

That is one of the highest awards given, and I congratulate you on receiving it. I think it is well deserved.

Dr. FELIX. Thank you, Mr. Chairman.

Mr. FOGARTY. Mr. Denton?

PATIENTS IN MENTAL HOSPITALS

Mr. DENTON. Doctor, I want to congratulate you on that award, too. Heretofore you have stated that, for the last 5 years, notwithstanding the fact that the population is increasing in this country, the number of patients in mental hospitals has declined. Has that continued in this past year, so that that will be 6 years now?

Dr. FELIX. Yes, sir. I spoke to that, as you remember. The number of patients in mental hospitals at the end of 1961 was 526,414. This compares with the number at the close of 1960 of 535,945. This is over a 9,000 drop, about 1.7-percent drop.

You might be interested in this. You remember in the years past I have told you what we have projected for the future on the basis of an 11-year experience, 1945 through 1955. We are over 108,000 below this projected figure. This is 17.1 percent less than we have projected it would be.

One figure I didn't give which might be of interest to you, if I have it here someplace, is the actual drop—this was a projection of 108,000. But the actual number less at the end of 1961 as compared to the end of 1955 is 32,508. This is 5.8 percent less.

One thing you did say that I think I would like, if I might, to get into the record. We do not know for sure that mental illness is on the increase. We do know that the population increases. If the percentage of people out of the population who became ill remained the same, there would be more people in hospitals just on the basis of actual increase in the population.

We do think that there are two groups in which there has been some increase—the people 65 years of age and over and—this is one we have to study some more—those under 15.

Mr. DENTON. Doctor, as I get it, the population in mental hospitals has declined 32,000 in 6 years.

Dr. FELIX. That's right.

Mr. DENTON. But naturally, because of the increase in population, we would expect more mental cases. So you have projected to show the increase and the number is how many?

Dr. FELIX. 108,000–plus.

Mr. DENTON. Below what the normal would have been on that projected basis.

Dr. FELIX. That is right.

COST OF MENTAL ILLNESS

Mr. DENTON. You have put in the record in the past the cost of mental illness to the Federal Government and to the States; and then you have put in the record how much is lost to the Federal and State Governments through the loss of taxes on what such people would normally have earned had they not been mentally ill.

Could you put those figures into the record again?

Dr. FELIX. I would be happy to, sir. You would like both the actual dollar expenditures and the estimate of what would have been lost in earnings and other more or less intangibles of this nature had they still been working.

Mr. DENTON. What I would like to find out is how much the public is losing because of mental illness. I think it would be a good idea to find out how much is lost in earnings; but I want to show how much the Government would lose in taxes and how much the States would lose in taxes on those earnings.

Dr. FELIX. All right, sir.

(The requested information follows:)

COST OF MENTAL ILLNESS

It is difficult to estimate the loss to the public, in product and in taxes, which is due to mental illness. At the end of 1961 there were 526,414 resident patients in public mental hospitals. If we assume that half of these people would be employed, if they were not mentally ill, and that they would have the average earnings for 1961, $4,850, the national product would be increased by $1.28 billion. Since each dollar of national product generates 20 cents in Federal taxes and 4 cents in State taxes, we can assume that the tax losses to Federal and State governments are $256 million and $52 million, respectively. These estimates refer only to persons hospitalized in public mental hospitals. There are still further losses due to mental illness among persons who are not in public mental hospitals. There is currently no basis for calculating these losses.

EFFECT OF NIH RESEARCH ON MENTAL ILLNESS

Mr. DENTON. A good many of the cures for mental illness have been discovered by research at the National Institutes of Health, haven't they?

Dr. FELIX. Either that conducted by our own scientists or that supported by our grant program. These two together, I think, account for a very significant proportion of the new discoveries.

Mr. DENTON. Nate Kline worked on Rauwolfia, didn't he?

Dr. FELIX. He has worked with phenothiazines, too; but he was the first person to work with Rauwolfia in this country.

Mr. DENTON. We have one institution that shows by rehabilitating disabled people these people are able to pay so much money in taxes. For every dollar the Government spends, they take in about $10 in taxes. While you can't claim all the cure in mental illness, you can claim a great deal of it.

Would it be possible to present figures to show how much research has benefited the Government and the taxpayers by decreasing the expense in caring for the people and by making those people rehabilitated taxpayers so they paid money to the Government? Could you get figures out on that, do you think?

Dr. Felix. I would try very hard. I would ask the indulgence of the committee—particularly Mr. Moyer, the clerk—because I may not be able to meet your 2- or 3-day deadline in getting this in. This is going to take some figuring.

I will try very hard to do it, but it will take longer than the 2- or 3-day deadline before the transcript has to come back.

RESEARCH PROJECT ON GOATS

Mr. Denton. In connection with this statement made about the monkeys, I think a very interesting case is one that you had some 10 years ago, when some newspaperman made light of the fact that you had a research project which investigated goats.

Dr. Felix. Yes, sir.

Mr. Denton. I believe they said it was to find out what made goats baa. I remember your explanation of that was splendid. But I think the most interesting thing about it is that that experiment enabled a doctor to tell when a man in action in the Korean war was going to suffer what in World War I we called shellshock and what in World War II we called combat fatigue, and which saved the Government a great deal of money.

Dr. Felix. You are absolutely right. That is exactly what happened.

REVIEW OF RESEARCH GRANT APPLICATIONS

Mr. Denton. Who passes on all these research projects?

Dr. Felix. This is what they call a double review system, Mr. Denton. A man applies for a grant. He outlines his project, what he wants to do, the method he is going to use, the hypothesis that he is testing; and he puts in a budget of how much he feels it is going to cost him and how many years it is going to take to do it.

This is reviewed administratively by the staff of the National Institutes of Health to determine which one of the institutes it should go to. Then it is assigned to an institute by the Division of Research Grants of the National Institutes of Health.

Mr. Denton. We have got that from Dr. Shannon up to this point. I want to get it from then on.

Dr. Felix. It is reviewed by a study section. A study section is a group of outside scientists, distinguished scientists from all over the United States, distinguished in that particular area. It may be pharmacology; it might be genetics or something else. They look over this application carefully.

Wherever it is needed, one or two of the members of that committee will go to the place where this person is going to carry on his research, talk to him, see what the situation is, and get a first-hand——

Mr. Denton. Are they government employees?

Dr. Felix. No, sir, only in that they are paid a consultant's fee on the days that they work. But they are not Government employees.

If there is a very specially qualified individual who happens to be a Government employee who is particularly qualified in that area, he may perchance be a member of one of these study sections. But this is just because he is an outstanding scientist and there wouldn't be more than one of those at any one time on some study section.

The study section, after reviewing this and discussing it among themselves—and I have seen study sections take 2 and 3 hours with one project; this is not always so, but where it is needed, they give it as much time as necessary. They work into the night. They meet for 3, 4, or 5 days and they may work way into the night every night until they go home, if the load is large.

They then make a recommendation as to whether this project should be approved or not and assign it a priority. That is, in their recommendation this is No. 1 on the list or No. 10 or something else. This, then, goes to the appropriate national advisory council.

In my case it would be the National Advisory Mental Health Council. There again it is reviewed, both from the point of view of the study section's evaluation of the case scientifically; but also from the point of view of policy. That is: Is this appropriately an area in which, in our case, the Mental Health Institute should be working? Are there other considerations other than the scientific ones which should be given thought?

They then vote to sustain the recommendations of the study section or not, as the case may be; and if to sustain, assign it a priority.

NATIONAL ADVISORY MENTAL HEALTH COUNCIL

Mr. Denton. Right there I want to ask you one question. Could you give us for the record the names of the people—not your study group, but your department's group——

Dr. Felix. The National Advisory Mental Health Council? Yes, sir.

Mr. Denton. And give us a short biography of who the men are.

Dr. Felix. Yes, sir, I will be happy to.

(This information may be found at p. 1007.)

Mr. Denton. Are they leaders in that field?

Dr. Felix. These are distinguished leaders in that field. As a matter of fact, Mr. Denton, one of them is a college president in your State, Dr. Russell Humbert of DePauw. He is a member of the Advisory Mental Health Council at the present time.

Under the law the Surgeon General may not authorize payment of any research application unless it is approved by a council. This is the legal body set up under the legislation under which we operate.

The Surgeon General, however, does not have to pay all of those approved, for, among other reasons, the most obvious one is there may not be enough funds to cover it so he can't pay them all, and he is not required to take what money he has and divide it up among all the approvals so nobody gets enough.

They go down the priority list in priority order as far as the money lasts and cut it off there.

RESEARCH GRANTS

Mr. Denton. How much of your appropriation is available for grants?

Dr. Felix. You mean of this year's appropriation, sir, for research grants?

Mr. Denton. Yes.

Dr. **Felix.** $42,748,000.

Mr. **Denton.** Of that $42,748,000, how far does that go in approving grants? What I would like to have is the number you get down to and how many approved grants you are not able to take care of.

Dr. **Felix.** That will pay this year about 1,600 of our approved applications for research projects.

Mr. **Denton.** How many will you be unable to take care of?

Dr. **Felix.** We are more fortunate than any other Institute this year. It will not take care of a very small number—less than a dozen. About $200,000 worth it will not take care of.

One of the reasons for this, I might say, is that the Mental Health Council is a very hard-boiled group. Our approval rate is one of the lowest approval rates of any of the councils. They only approve about 32 or 33 percent of all applications. One reason they stay within this is because they are very tough.

MENTAL HEALTH TRAINING

Mr. **Denton.** In that same connection we found a number of years ago that there were not enough psychiatrists or doctors specializing in mental health. One of them told me in a hospital in my home State that he had 600 patients. He said if he had time, he was sure he could cure a great many of them; but as it was, he could only give a lick and a promise.

Have you done anything about correcting that situation?

Dr. **Felix.** Yes, sir. There has been a steady increase in the number of not only psychiatrists, but other types of professional personnel over the last 10 years.

I can supply the figures for that, if you wish. However, there is one interesting thing that has happened here. That is, as we have supplied more, the demand for them has increased. So we are not as far ahead as the gross figures would show.

Also I should add here that there is an increasing tendency of these people to enter public service, so that the pool of those in private types of practice is not increasing at the same rate as those in public service.

Mr. **Denton.** In just talking to this doctor who told me he had 600 patients, he said if he had time, he could cure a good many of them, but he couldn't. It struck me that it would be pretty good business for the Government to train a man at its own expense to do this kind of work, rather than keeping these people as patients.

What could be done to make that program more efficient or more effective?

Dr. **Felix.** There is no question in my mind that if there were more people available to treat these people, many more people could get out of the hospital if the case load were smaller and the doctors and the social workers, the psychologists, the nurses, and all of these people could spend more time with each patient.

It would be cheaper to adequately train them and to pay them an adequate salary than it would be to keep the people in the hospital for an indefinite number of years, who will remain in because they are not there to do the job. I think I can back this up with figures.

COST OF TRAINING ADDITIONAL PSYCHIATRISTS

Mr. DENTON. How much more do you think should be spent for training psychiatrists or people dealing with mental health than you are spending now?

Dr. FELIX. You are asking me this without regard to anything except if I were coming here from the outside, what would be my figure?

Mr. DENTON. Yes.

Dr. FELIX. I don't want any mistake——

Mr. FOGARTY. No; we have cleared this with the Secretary and the Surgeon General. When you are asked a question like that, you are free to give us your personal, professional opinion.

Dr. FELIX. Our best estimates are that, as we are now pretty well tooled up, if it were thought wise by the administration and by the Congress, considering everything else and what proportion of all of this should go to mental health, we could use something around $50 million in 1963.

We could very well use an increment of between $10 and $15 million a year following that for at least the next 5.

I wouldn't want to project beyond that because I think my projections would be so out of date they would have to be revised. But by that I mean $65 million the next year, $80 million the next year, and so on.

Mr. DENTON. Doctor, when people are treated for mental illness either by shock treatment or drugs, isn't it necessary that you have a psychiatrist to follow up that treatment?

Dr. FELIX. Yes, sir.

Mr. DENTON. And some people can be treated by a psychiatrist without the help of drugs or shock, too, can't they?

Dr. FELIX. Yes, sir.

Mr. DENTON. Do you think the training of psychiatrists is very important toward the curing of mental illness?

Dr. FELIX. Absolutely. This is the captain of the team, no matter how you look at it.

INCREASED CURE RATE FOR MENTAL PATIENTS

Mr. DENTON. Did you say that the number of people who have been in mental hospitals over 5 years and are now being cured is increasing?

Dr. FELIX. Yes, sir. I said in New York State they have done a study directed toward determining the number of schizophrenic patients who had been in their system for more than 5 years. They did this because, as you remember, the statistics over the years have been that if a person stayed for 5 years or more, his chances of getting out were less than 1 in 100.

They find that the number of patients who have been in the hospital 5 years has dropped 20 percent over the last 5 years. That is, there are 20 percent less of these 5-year-or-longer patients in the hospital in 1961 than there were 5 years before that.

Mr. DENTON. How do those who have been in less than 5 years make out?

Dr. FELIX. I don't have the data on those. I may be able to get it for you. I don't have it here.

Mr. MARSHALL. Dr. Felix, what is the reason for an increase of $487,000 in "Other services" as shown in the table on page 104 of your budget?

Dr. FELIX. That item, sir, is composed of three items which are: renovations at the Addiction Research Center, renovations at the Clinical Neuropharmacology Research Center, and contracts for biometrics research with such agencies as the Bureau of the Census.

INCIDENCE AND COST OF MENTAL ILLNESS

Mr. FOGARTY. Dr. Felix, would you also submit a statement on the incidence and cost of mental illness?

Dr. FELIX. Yes, sir.

(The requested report follows:)

INCIDENCE AND COST OF MENTAL ILLNESS

NATIONAL INSTITUTE OF MENTAL HEALTH

Statistics of the annual number of deaths and total current number of disabilities caused by each of the major diseases dealt with in the National Institute of Mental Health, and the estimated annual cost to the Nation

I. DEATHS DURING 1959 FOR WHICH SOME FORM OF MENTAL ILLNESS WAS GIVEN AS THE CAUSE (NATIONAL OFFICE OF VITAL STATISTICS) [1]

Category:	*Number*
Psychoses	1,539
Psychoneurotic disorders	90
Personality disorders	2,767
Epilepsy	2,069
Total	6,465

[1] In addition, there were 18,630 suicides. The number of these for which mental disorder was the cause is unknown.

II. DISABILITIES FROM MENTAL ILLNESS

There are no sound nationwide data available on the number of disabilities resulting from mental illness. The following is the number of patients receiving care for mental illness or mental deficiency in the various types of psychiatric facilities at some time during 1960. If it is assumed that each of these individuals was disabled at some time during the year, this would then represent a minimum estimate of disability.

Type of facility:	*Number of patients receiving care during 1960*
State and county mental hospitals	776,729
Veterans' Administration hospitals	117,130
Private mental hospitals	86,844
General hospitals with psychiatric facilities	203,627
Public institutions for the mentally deficient	[1] 170,384
Private institutions for the mentally deficient	9,962
Outpatient psychiatric clinics	[1] 502,000
Total	1,866,677

[1] 1959 data (revised); data for 1960 not yet available.

NOTE.—These data are based on reports received by the National Institute of Mental Health from State agencies, hospitals, and clinics.

III. ESTIMATED ANNUAL COST TO THE NATION

A. Direct cost:

1. To Federal, State, and local governments for care of patients, fiscal year 1961 [1]	$2,037,024,000
2. To private agencies and individuals	(2)

[1] Based on data received from Federal and State agencies responsible for the care of psychiatric patients.
[2] Not available.

Mr. FOGARTY. Doctor, do you have anything else you want to say before you leave?

Dr. FELIX. No, sir, I don't. Thank you very much for hearing me.

Mr. FOGARTY. Thank you. I think it was one of the best reports we have had on mental health.

Dr. FELIX. Thank you, sir.

Mr. FOGARTY. We shall reconvene at 1:30.

(The following additional data was submitted at the request of the committee:)

HIGHLIGHTS OF PROGRESS IN MENTAL HEALTH RESEARCH, 1961

INTRODUCTION

Research in the field of mental health and the mental illnesses spans a broad spectrum of physiological, psychological and sociological sciences.

The problems posed by mental disorders and the behavioral and physical dysfunction that result from them are extremely complex, and are susceptible to no single solution. The very diversity of the mental illnesses, and the high toll they exact from our society, make the attack upon them one of the major scientific challenges of our time.

Although much progress has been made toward an understanding of many aspects of mental and emotional disorders, the etiology of mental illness is as yet not fully understood. Research on schizophrenia, for example, has suggested many leads and contributive causes; significant correlations between physiological and behavioral change have been discovered. But the ultimate answers to the perplexing problems of these relationships remain to be found through continuing research along many fronts involving many disciplines.

In the search for answers to the mental illnesses, a fuller understanding of man's normal functioning as a social, psychological and biological entity is necessary. For this reason, many basic studies in this field are concerned with increasing our knowledge of the complex relationships of the human mind with its environment.

Furthermore, in spite of the gaps in knowledge regarding the mental disorders, much has been learned about ways in which these illnesses may be alleviated. An important aspect of research in this field is concerned with means of utilizing new knowledge that has been gathered regarding prevention, treatment, and rehabilitation.

Selected research findings of the past year are presented in this report. The research includes studies conducted in the Institute's own laboratories, as well as in many nongovernmental research centers throughout the country that have received Institute support.

NOTABLE MENTAL HEALTH EVENTS OF THE YEAR

Several significant events with far-reaching implications for mental health occurred during the year.

A notable milestone was publication of "Action for Mental Health." The report presents the findings of a 6-year study of the Joint Commission on Mental Illness and Health, authorized by Congress in 1955 to evaluate the needs and resources of the mentally ill in the United States and make recommendations for a national mental health program. The Commission included representatives of 36 national organizations concerned with this field.

Among the findings:

> The demand for public mental health services is still largely unmet, in spite of the great gains scored during the past decade.

Probably no more than 20 percent of the 277 State mental hospitals have participated in innovations designed to make them therapeutic as contrasted to custodial institutions.

The average proportion of general State expenditures allocated to mental hospitals has declined in recent years.

An average of $4.72 per patient per day is spent by State hospitals, as compared with $31.16 for community general hospitals and $12 or more for Veterans' Administration psychiatric hospitals.

The persistent attitude that schizophrenia is incurable is false. With proper treatment, the schizophrenic has a 3-in-5 chance of leading a useful life in the community.

The rejection of the mentally ill by society has been a major factor in the lag in effective treatment. More helpful attitudes must be created.

Among the recommendations:

There is a need for more long-term and basic research in mental illness.

In patient care, emphasis should be given to breaking down barriers between hospital and community; providing more immediate help and extending the care of mental patients through clinics and other agencies; improving the therapeutic milieu in the mental hospital; and developing after-care programs.

The pace of recruitment and training for all categories of mental health personnel should be accelerated.

Efforts should be made to increase the use of nonmedical mental health workers with aptitudes, sound training, practical experience and demonstrable competence to perform mental health counseling under professional supervision.

More adequate intensive treatment of acutely ill patients is needed: one fully-staffed mental health clinic is suggested for each 50,000 population.

More psychiatrists in private practice should be encouraged to participate in community clinic services.

Psychiatric units in all community general hospitals with more than 100 beds are desirable.

New State hospital construction should be confined to intensive treatment centers of 1,000 beds or less.

Large State mental hospitals should be converted into combined chronic disease centers within the next 10 years.

A program should be eventually developed whereby the Federal Government shares with the States the cost of mental patient services, over and above current and future programs of Federal grants-in-aid for research and training. (Action for Mental Health, Basic Books, Inc., New York, 1961.)

A special Governors' Conference on Mental Health was held in Chicago in November to discuss directions and emphases for effective planning for more adequate care and treatment of the mentally ill. At the 2-day meeting the Governors expressed their concern for what they described as "the No. 1 health problem of the Nation" by drafting resolutions calling for accelerated action. They commended the Joint Commission for its study and endorsed the concept that Federal, State, and local government as well as private and voluntary efforts must be combined to achieve goals sought.

A balanced State program, they stated, should include: prevention and early casefinding and treatment; a complete range of community-based services, emphasizing continuity of treatment; active treatment rather than custodial care during hospitalization, rehabilitation, and aftercare services; special services for patients suffering from conditions closely related to mental illness such as mental retardation, alcoholism, delinquency, aging; research, recruitment, training, and imaginative utilization of paid staffs and volunteers; effective centralized responsibility for all State-supported services; and involvement of professional associations and voluntary mental health and social agencies in planning and providing the highest quality of care for all mental patients.

Another important event was publication of the "Report of the Surgeon General's Ad Hoc Committee on Planning for Mental Health Facilities." Its major recommendations include: (1) The establishment of community-based mental health facilities offering a wide spectrum of services, as part of a coordinated system of statewide health services; (2) stimulation of comprehensive planning for mental health facilities by action of the Governors of the States, through designation of an existing agency or appointment of a planning body of professional and citizen groups; (3) enactment by the States of enabling legislation to encourage development of needed mental health facilities. ("Planning of Facilities for Mental Health Services." PHS publication No. 808. Government Printing Office.)

A comprehensive attack on mental retardation was launched in October with the appointment by President John F. Kennedy of a panel of 27 experts to explore possibilities for its prevention and cure.

The panel will survey biological, psychological, educational, vocational, and sociocultural aspects of mental retardation and their impact upon each stage of human development. It will determine the adequacy of existing programs and possibilities for greater utilization of current knowledge. Recommendations of the panel will be submitted to the President in December 1962.

BIOLOGICAL STUDIES

Biological research in mental illness involves all of the techniques and disciplines available to the physical and clinical sciences. It ranges from basic research on enzymatic action in vitro to clinical chemistry studies in man.

At one end of the spectrum studies are being conducted on systems so simplified that they may contain only few substances derived from living material. At the other, investigations are being pursued on the total intact human being, covering a wide range of human behavior, both abnormal and normal.

Evidence that certain forms of mental illness and retardation are rooted in physical disease or dysfunction has stimulated a variety of approaches to the study of the subtle and complicated metabolic processes of the body. Evidence is accumulating that biogenic amines and other substances present in the brain have major effects on the behavior through their action on the nervous system. Extensive research is underway regarding the synthesis, degradation, and distribution of these amines in the body and brain, in an effort to determine whether abnormalities in the metabolic processes may play some role in the etiology of mental illness, particularly schizophrenia.

Metabolic studies

Indole metabolism and schizophrenia.—Despite longstanding controversy, the idea that metabolism of the indole compounds may have implications in schizophrenia continues to persist. In a review of research on biochemical aspects of schizophrenia, an NIMH grantee recommends further investigations of these fundamental chemical structures widely present in the body.

That the indole compounds have many ramifications in the physiology and biochemistry of behavior is evident from research along such diverse lines as the effect of indolic compounds on the psyche, on electrical activity and enzymatic systems of the brain, on nerve cells in tissue culture; toxic effects on animals of indolic extracts from body fluids of the mentally ill; and patterns of excretion of urinary indoles in schizophrenic patients and normal controls.

No fewer than 10 laboratories throughout the world, a survey discloses, have reported consistent agreement on the more frequent occurrence of a specific indole compound in the urine of schizophrenic patients than in normal controls.

Controversy has arisen over results from urinary studies interpreted without due consideration of medication, dietary differences, excretion products from intestinal bacteria, and other complicating factors having to do with institutionalization and normal variation. But some recent research studies, particularly those dealing with the urinary glyoxylic acid test and the excretion of 6-hydroxyskatole sulfate, have attempted to correct for such factors. These studies still demonstrate increased excretion of urinary indoles in schizophrenia.

The findings with 6-hydroxyskatole sulfate are of special interest in view of the recent claim that the 6-hydroxylation of the psychotogen diethyltrytamine is responsible for inducing behavior disorders in rats.

Surprisingly little is known of the cellular metabolism of indoles, particularly skatole and hydroxyskatole. The recent discovery that the major route of hydroxylation of skatole in man is through the 6 position is challenging. It is possible that the process of 6-hydroxylation may be an aberrant metabolic pathway for the indoles in general and at the same time associated with the development of behavioral disturbances.

Attempts to relate indole metabolism to mental illness, particularly schizophrenia, have been many but are at best inconclusive and no direct relationship has been demonstrated. But abnormal metabolism is well delineated in three diseases having mental symptoms: phenylketonuria, Hartnup (Hart's or

H) disease and pellagra. Despite the controversial aspects, reports of abnormal indole metabolism in mental illness are sufficiently numerous to warrant further studies.

(NIMH Grantee Dr. Herbert Sprince, Veterans Hospital, Coatesville, Pa., and University of Pennsylvania School of Medicine. Reported in Clinical Chemistry.)

Indole in urine identified.—The same investigator and his associates have further identified chemically as indoleacetamide the unknown indole found in significant levels in urine specimens from schizophrenics.

Subsequent to studies indicating statistically significant differences in the relative presence of indole in schizophrenics as compared to normal controls, the investigators proceeded to isolate and identify the indole involved. They obtained a compound which, through a series of chemical tests, was found to have the same qualitative and quantitative characteristics as indoleacetamide.

The indoleacetamide found, the scientists believe, was probably derived through ammonolysis from the major parent metabolite indoleacetylglucuronic acid, as has been suggested by other investigators. They raise the question whether an increased excretion of the glucuronide conjugate of indoleacetic acid as measured by indoleacetamide may occur in schizophrenia. Further development of precise quantitative assays for indoleacetamide and indoleacetylglucuronic acid in human urine is presently underway. (Reported in Journal of Laboratory and Clinical Medicine.)

Psychoactive compounds made by new enzyme.—An NIMH investigator has discovered an enzyme in the tissues of the rabbit that converts two compounds normally occurring in man into substances known to cause psychotic behavior.

Two substances known to cause psychoticlike effects in humans are bufotenine and dimethyltryptamine. Both are ingredients of cohoba, a snuff used by Indian tribes in Haiti that provokes exotic behavior during religious rites. But neither has been confirmed as occurring naturally in humans, although bufotenine has once been so reported.

Recent experiments with rabbit tissues have disclosed that serotonin and tryptamine, two biogenic amines present in man as well as in rabbits and other animals, can be converted into bufotenine and dimethyltryptamine, the psychotomimetic compounds.

Further investigation by this scientist has revealed that the metabolizing agent is an enzyme in the rabbit's lungs. The enzyme has not been named as yet because it reacts to so many compounds.

The finding that the enzyme has the capacity to change serotonin and tryptamine to bufotenine and dimethyltryptamine in vitro will be pursued further to ascertain whether it actually does so in vivo. (Dr. Julius Axelrod, NIMH. Reported in Science.)

Hallucinations produced by normal body metabolites.—Research conducted during the past year with human volunteers at the NIH Clinical Center has substantiated findings from studies on experimental animals indicating that compounds occuring normally in the body can be converted to substances that induce hallucinations and other perceptual and emotional disturbances.

Scientists have found that several simple derivatives of tryptamine, as intermediate substance in certain metabolic processes in the body, produce hallucinations and other mental disturbances and autonomic symptoms when given orally or by injection.

The symptoms appear rapidly, but last only a relatively short time, 1 to 3 hours, compared to from 6 to 10 hours for similar reactions produced by lysergic acid diethylamide (LSD–25) or mescaline. This indicates a more rapid metabolism for the tryptamine derivatives and a more direct action on the central nervous system.

In following the fate of these derivatives in the body, it was found that the first change took place in the liver. It was unexpectedly discovered that the liver, considered to be the most important organ in detoxifying foreign substances, transforms these tryptamine compounds by enzyme action into derivatives that are psychologically more active than the parent compound. These metabolites, reaching the brain by the bloodstream, produce psychological phenomena before they are detoxified in the liver and eliminated through the kidneys.

Another important observation was the striking difference in individual reaction to one of these derivatives, N. N-diethyltryptamine (DET), both in the symptoms and their intensity, when similar doses were given. Suspecting that the rate of the enzymatic process hydroxylation was responsible for these individual differences, the researchers conducted tests that showed a direct relation between the intensity of reaction and the amount of the metabolite excreted in the urine.

Since tryptamine is one of the many amines normally occurring in the body and can serve as a substrate for the hydroxylation reaction, the possibility is suggested that the reaction may play a role in the biochemical mechanism leading to mental changes. (Dr. Stephen Szara, NIMH. Reported in Federation Proceedings.)

Fate of catecholamines.—The enzyme chiefly responsible for metabolizing the circulating catecholamines, epinephrine (adrenalin) and norepinephrine, was identified as catechol-O-methyl transferase, instead of moneamine oxidase as previously believed; and the metabolic products were isolated in previous research at NIMH. Recent investigations have thrown new light on the mechanisms and metabolic fate of these hormones.

Radioactive epinephrine and norepinephrine injected into the blood stream of animals was found to be rapidly but unequally taken up by tissues. Only a negligible amount was found in the brain, indicating a blood-brain barrier to the passage of these compounds.

Two hours after their administration, the amount of hormones in the heart, spleen and adrenal glands was the same as it had been 2 minutes after the injection, indicating that these tissues retain the hormones for long periods of time, presumably due to binding to the tissues which protects the hormones from enzymatic attack. When the hormones are released again, they become physiologically active.

When the sympathetic nerves were destroyed by denervation, the uptake of radioactive norepinephrine by tissues was profoundly reduced. These experiments indicated that circulating norepinephrine was taken up by the sympathetic nerve endings and stored there.

This property enabled investigators to introduce radioactive epinephrine into the sympathetic nerve endings and study its fate upon discharge from these nerves.

That norepinephrine is the hormone liberated from nerve endings has been known for some time. The study of what became of this important hormone in the sympathetic nervous system was undertaken by first introducing radioactive norepinephrine into the spleen, and perfusing it with the blood of an animal free of the radioactive hormone. When the isolated splenic nerve was stimulated electrically, radioactive norepinephrine was discharged into the venous outflow of the isolated spleen, together with small amounts of normetanephrine, the O-methylated metabolite of norepinephrine.

These observations indicate that upon stimulation, part of the stored radioactive norepinephrine was discharged into the blood, part taken up again by the nerve endings, and part converted by enzyme action to its metabolite, normetanephrine. (Drs. Julius Axelrod, George Hertting, L. G. Whitby, and H. Weil Malherbe, NIMH. Reported in Nature, Journal of Pharmacology and Experimental Therapeutics, and Science.)

Serotonin and behavioral change.—Recent findings by NIMH grantees indicate that it is now possible to measure quantitatively the behavior of an animal and correlate the changes observed with biochemical and physiological parameters. Studies on pigeons have shown that a behavioral change is associated with increased levels of free serotonin in the brain.

The investigators found that the metabolic products of tryptophan, which are precursors of serotonin, are associated with these changes, and that intramuscular injections of serotonin smaller than those of its precursor could produce the same change.

The dose of chemical injected was directly related to the behavioral change observed. As the dose increased, the change in behavior increased. This consisted of pauses in pecking behavior, during which period the birds usually stood immobile, but exhibited bodily tremors, headshaking, and frequent shifting from one foot to the other

The investigators further demonstrated that the behavioral change was associated with the level of serotonin in the brain and not serotonin located in the peripheral organs of the body.

These findings contribute to an understanding of factors involved in adaptive behavior, and suggest that variation in brain chemistry may be a major determinant of the variation in adaptive behavior among normal individuals. Interference in the metabolic pathways, they indicate, may result in abnormal adaptive behavior. (Drs. M. H. Aprison and C. B. Ferster, University of Indiana. Reported in Journal of Neurochemistry.)

Effect of drugs on Metabolism of catecholamines.—Many drugs affect the physiological action of the catecholamine hormones epinephrine (adrenalin) and norepinephrine, but little has been known of their mode of action at the biochemical level. Reserpine, chlorpromazine and imipramine; the sympathomimetic amines, tyramine and amphetamine; cocaine; the adrenergic blocking agent phenoxybenzamine; and hypotensive drugs such as guanethidine, lower the concentration of injected radioactive norepinephrine in the heart, spleen and adrenal glands of most animals. Most of these drugs also speed up the metabolism of the hormone in the whole body.

These drugs have many actions and could produce a common end result by three different mechanisms: by (1) lowering the level in the tissues by blocking the entry of the hormone into the storage sites; (2) preventing the binding action there; or (3) releasing it into the circulation; or by a combination of all three.

In recent studies, reserpine, amphetamine, d-adrenalin and phenoxybenzamine were found to reduce the amount of radioactive norepinephrine in the heart tissues when given subsequent to as well as prior to the hormone. The same action had previously been observed regarding tyramine. These findings suggest that those drugs release the bound hormone from storage sites.

Further studies have indicated that chlorpromazine, imipramine, cocaine, and dichlorisoproteronol block the uptake of the hormones into storage sites. Tests showed that these drugs do not release the catecholamine hormone once it is bound to the tissues. (Dr. Julius Axelrod, George Hertting and Lincoln Potter, NIMH. In press, Nature).

New light on thyroid function.—Research by NIMH investigators on protein synthesis has thrown new light on the role of thyroxine as regulator of utilization of energy.

The thyroid gland and its hormonal secretion, thyroxine, have long been known to affect growth and development. When there is deficient thyroxine in immature animals there is retarded growth, and in man evidence of mental retardation also.

Previous theories of action of thyroxine have emphasized the effects on the oxidation of foodstuffs, and the efficiency of deriving biologically useful energy from these oxidations.

Several considerations led NIMH researchers to suspect that the role of thyroxine was more involved in regulating the utilization of energy than in its generation. Growth and development are processes that require energy and appear to be dependent on thyroxine. The investigators therefore studied the effects of thyroxine on protein synthesis because this is probably the major chemical process involved in growth and development.

They have observed that thyroxine stimulates synthesis of protein in liver preparation obtained from both young and old adult rats.

They also noted that in immature brain in freshly weaned rats, thyroxine had a similar effect on protein synthesis as in liver.

On the other hand, in adult brain in which protein synthesis is a much slower process than in the developing brain, the thyroxine does not seem to have any notable effect.

This new concept of a possible role for thyroxine in synthetic processes may influence the thinking of investigators in this field and give a new direction and impetus to thyroid research. (Drs. Louis Sokoloff and Seymour Kaufman, NIMH. Reported at Third International Neurological Symposium.)

Brain research

Mechanisms for feeding, sex, and anger contiguous in brain.—In view of the complexities of sociosexual behavior it is a curious fact that until recently there was little evidence of localization of sexual function in the cortex and higher centers of the brain. In investigations concerned with this problem the response of genital tumescence in the monkey has been used as one indicator that a brain structure is involved in sexual behavior.

In summary, positive loci for the sexual response have been found in parts of three cortico-subcortical subdivisions of the limbic system: 1) they involve projections of the hippocampal cortex to parts of the septum, anterior thalamus and hypothalamus; 2) they are located in parts of a neural circuit comprising the mammillary bodies, mammillothalamic tract, anterior thalamic nuclei and anterior cingulate cortex, 3) they are found in the medial orbital cortex, the medial part of the medial dorsal nucleus of the thalamus and regions of their known connections.

In regard to this last finding it is of interest to recall that frontal lobotomy which severs the connections between the medial dorsal nucleus and the orbitofrontal cortex, sometimes results in bizarre, uninhibited sexual behavior.

In parts of the brain stem it has been found that structures involved in the sexual response lie next to others concerned with feeding and combative behavior. For example, within the space of a millimeter one may pass from a point at which stimulation results in the sexual response and an apparent state of placidity, to a point at which stimulation elicits the sexual response in conjunction with angry or fearful vocalization and the showing of fangs. When the electrode is advanced a fraction of a millimeter further, only the angry or fearful manifestations occur during stimulation, but are followed by the sexual response when stimulation is terminated. These and other findings might be interpreted as indicating a close anatomical and functional organization of excitatory and inhibitory mechanisms involved in feeding, sexual, and combative behavior. They suggest mechanisms which might mediate such forms of psychoses as pyropathia (sexual incendiarism), as well as many other forms of behavior in which feeding, fear and, anger are associated with sexual manifestations. (Drs. Paul D. MacLean, NIMH, and Detlev Ploog, visiting scientist, University of Marburg, West Germany. Reported at AAAS and in press, Journal of Neurophysiology).

Hunger and thirst centers in brain.—Research on the functional localization in the brain of the mechanisms of eating and drinking has heretofore largely focused on the hypothalamus: the lateral area in the initiation of the feeding, and the ventromedial area in the cessation.

However, recent evidence from a study by NIMH scientists attempting to map in monkeys the areas from which food ingestion and ejection could be directly elicited by a electrical stimulation, has indicated that hunger-satiety mechanisms are represented not only in the hypothalamus but in portions of the limbic system and thalamus as well.

Ten satiated animals were induced to eat and drink by electrode stimulation at 99 points in the brain outside of the hypothalamus, including the olfactory tubercule, medial preoptic areas, substantia innominata, and amygdala. The responses were similar to those produced by stimulation of the lateral hypothalamus. Similarly 7 animals were induced to remove food from their mouth and to stop eating, when stimulated from 113 points outside the ventrol medial area, including the lateral hypothalamus, substantia innominata and medial preoptic area.

It is of interest to note that motivational analysis suggests that the electrical stimulations evoking intake and ejection reactions are rewarding for the animals, since they will work to obtain this stimulation. (Drs. Bryan W. Robinson and Mortimer Mishkin, NIMH. Reported in Federation Proceedings.)

Map of monkey brain completed.—The first stereotaxic atlas or three-dimensional map of the brain of the squirrel monkey, *Saimiri sciureus*, has been completed by NIMH researchers.

The squirrel monkey has proved a particularly useful primate for neurophysiological research. It is relatively inexpensive, friendly and easily handled by one person, and adapts well to laboratory life and requirements. Although its body weight is comparable to that of a guinea pig, its brain is almost as large as a cat's. Readily available from South and Central America, the animal is characterized by a large occipital lobe, a nonprehensile tail, a brain-to-body weight ratio greater than man's, and a strongly communal or tribal life pattern.

The Atlas has 76 illustrations showing the location of various centers below the surface of the brain. Besides photographs of slides, it contains graphs showing the variations in position of certain brain centers. Although some variation occurs in any group of squirrel monkeys, accuracy for a single point in the brain will fall within 1.5mm. in more than 90 percent of the animals. This degree of accuracy is about the same as in the cat and much greater than that usually found in other species of monkeys. (Drs. J. A. Gergen and P. D. MacLean, NIMH. In press, Government Printing Office.)

Cortical excitability cycles.—NIMH grantees report results of preliminary experiments showing that it is now possible to measure certain neurophysiological phenomena directly in man instead of using laboratory animals and translating the findings to man. They have succeeded in measuring the electrical activity of the cerebral cortex in response to sensory stimulus (sensory evoked cortical potentials) without implanting electrodes beneath the scalp.

Data were obtained from multiple tests on 56 subjects, 32 of whom were psychiatric patients. The electrodes were placed on the head in specific areas depending on the response desired.

The potentials evoked by electrocutaneous stimulation consisted of a relatively constant initial response of brief duration, followed by secondary waves that continued for relatively long periods. These secondary waves were seemingly influenced by psychological factors.

Varying the stimulation intensity produced evidence that the first measurable evoked cortical potential occurs at the sensory threshold, and the size of the potentials is related to the intensity of the stimulus. Since this relationship was found regularly in a group of 24 subjects, the researchers believe it may be valid to use the cortical-evoked potential as an objective sign of sensory awareness in the unanesthetized patient.

In another study, the scientists used a photographic averager of the sensory-evoked potentials, and from measurements obtained evolved a method of representing cortical excitability cycles in curves on a graph. Measurements obtained from cats with implanted electrodes showed similar curves.

The major objective of this research is to compare cortical excitability cycles of normal human subjects with psychotics. Initial tests showed that the psychotic depressive patients failed to show the early peak of excitability shown by normals. Further, curves of a patient indicated changes resulting from electrotherapy. The pretreatment curve was flat and characteristic of a depressed patient, with no marked change in the curve during treatment, and a normal curve after successful treatment. The psychiatric implications of this research will be further explored. (NIMH Grantees Drs. Charles Chagass and Marvin Schwartz, College of Medicine, State University of Iowa. Reported in Journal of Neuropsychiatry.)

Neurophysiological studies

Near insight on mechanics of hearing.—Although the Nobel Prize was recently awarded for research on how the organ of hearing, the cochlea, functions, insight into the mechanism of origin of nerve impulses serving hearing is still incomplete. It is known that sound waves set up movements of fluid columns and membranes within the cochlea. Recent studies by an NIMH scientist contribute to insight as to how this mechanical perturbation gives rise to nerve impulses. The hair cells to which the auditory nerve fibers are closely attached, lie across a strong electrical field. This field appears to be supported to an important extent by metabolic activity in a vascular organ lying within one of the fluid chambers of the cochlea. Investigation of the general mechanisms of excitability of membranes suggest that the excitability of the hair cells may be vastly enhanced by virtue of their exposure to this strong electrical potential. This may be one of the features of the ear which enables a person to hear very low-intensity sounds, such as would cause displacement of the ear drum by a distance measured in terms of atomic diameters. (Dr. Ichiji Tasaki, NIMH. Reported at Symposium on Auditory Mechanisms.)

New technique aids theory of cell permeability.—A new theory explaining the permeability of the surface membrane of nerve cells has been developed by NIMH scientists. The theory is based on recent experiments carried out on giant axons of the common squid.

These giant axons offer a unique opportunity for studying movements of various chemical substances across the surface membrane of the nerve cell. Although full-grown squid are only about 1 foot long, some of their axons in the stellate nerve—innervating the muscle for jet-propulsion in case of enemy attack—are exceptionally large, the diameter being 1/50 to 1/25 of an inch as compared to 1/10,000 to 1/1,000 of an inch for most animals. A single giant axon of this type can be removed from a squid and cleaned of the surrounding tissue.

A technique has recently been perfected by which the major portion of the substance (axoplasm) inside the surface membrane can be removed without destroying the normal function of the axon to conduct nerve impulses.

Using a glass pipette introduced at each end of such a hollow axon, it was found possible to bathe the interior of the axon with various artificial solutions containing radioisotopes. Since the surface membrane is to some extent permeable, the sea water surrounding such a perfused axon also becomes radioactive. Comparing the radioactivity inside the axon with the radioactivity in the surrounding medium, it is possible very accurately to determine the permeability of the membrane to various substances Conversely, it is possible to introduce radioactive material into the sea water surrounding such a perfused axon, and determine how rapidly the substance in question is transported across the surface membrane from outside to inside.

It was found by this technique that positively charged ions and radicals (sodium-, potassium-, guanidine-ions, etc.) are transported across the membrane far more readily than negatively charged particles (choloride-, bromide, sulfate-ions, etc.). When the axon is artificially stimulated by electrical impulses, the transport of positively charged particles is profoundly accelerated while the movement of negatively charged particles remains uninfluenced.

These basic studies, still underway, strongly suggest that the surface membrane of te squid axon has a fixed negative charge, exerting repulsive force upon negatively charged particles and permitting positively charged particles to jump from one negative site to the next. The existence of such a negative charge in the membrane had been previously suggested by a few investigators but without any supporting experiments. The NIMH investigations provide a consistent theory which explains how excitation progresses in such a membrane with fixed negative charge. (Drs. I. Tasaki and C. S. Spyropoulos, NIMH, and Dr. T. Teorell, Visiting Scientist, Univ. of Uppsala, Sweden. Reported in American Journal of Physiology.)

Transmission of acquired characteristics.—Experiments with planaria, the lowest creatures on the evolutionary scale possessing a primitive brain and central nervous system, indicate that there is a transmission of acquired "learning" in asexual reproduction.

A group of NIMH grantees at the University of Michigan conditioned flatworms to contract when exposed to light by giving them an electric shock following exposure to a flash of light. After repetition, the worms contracted in response to the light alone. Then the worms, which have remarkable regenerative powers, were cut in half. When the tails had grown new heads and vice versa, the regenerated worms showed a significant retention of the conditioned reflex.

This result raised the question of how the tails could retain as much as the heads which contain the makeshift brain of the flatworm. This and the question of whether successive generations of cut and regenerated worms could retain a conditioned response were the subjects of another experiment in which flatworms were cut in half and only the head was conditioned. Then the head was allowed to regenerate. The resulting creature—anatomically distinct from the original head—retained a significant amount of learning. One theory of how such retention is possible suggests that some kind of chemical conditioning takes place in the planaria which is transmitted to succeeding generations. This was tested at the University of Rochester by having conditioned worms regenerate in a liquid containing RNASE, a chemical that breaks up ribonucleic acid, a substance which plays a decisive part in heredity. The tails of these worms were unable to retain previously acquired learning.

Further research is being devoted to the role of chemistry in acquired learning and the question of whether there is a similar transmission of learned experiences through sexual reproduction in flatworms. Sexual transmission of acquired characteristics in higher animals has traditionally been thought to be impossible. (NIMH grantees Dr. James V. McConnell, Allan L. Jacobson, Reeva Jacobson, and Margaret L. Gray, University of Michigan. In press, Psychological Bulletin.)

Psychopharmacology

Early clinical screening of new drugs.—A program to speed the development of new drugs to combat mental illness has been developed by the NIMH Psychopharmacology Service Center. It provides support for early clinical evaluation of new drugs potentially useful in the treatment of psychiatric conditions. Goal of the program is to make it possible for patients to benefit more promptly from drug discoveries.

Recently, the number of new compounds showing promise in animal testing has far outstripped the facilities for adequate clinical investigation. By making possible more extensive clinical trials, the new special program should help solve this problem.

The evaluations are underway at 19 hospitals where the drugs are being used to treat chronic mental patients who do not respond to existing therapy. About 75 new chemical compounds are being studied in an effort to determine their effectiveness and the kinds of patients they will help.

The program is a cooperative effort involving pharmaceutical firms, hospital investigators, and the NIMH.

Selected experienced scientists are receiving grant support for the necessary staff to conduct more extensive research. Clinical facilities are provided by the hospitals, and the drugs are supplied by pharmaceutical houses. Close liaison and technical assistance is being given by the Psychopharmacology Service Center.

Psychopharmacology abstracts.—A new abstracting service to assist scientists in keeping abrest of developments in psychopharmacology was developed during the year by the NIMH Psychopharmacology Service Center. A monthly publication, Psychopharmacology Abstracts, provides coverage of worldwide current literature in this field. A contract for the abstracting service has been let to a nonprofit organization specializing in the preparation of abstract journals. The literature search is being conducted under supervision of the PSC staff.

Primary reason for launching the abstracting service is the breadth of the field of psychopharmacology which straddles many traditional scientific disciplines—psychiatry, medicine, anthropology, psychology, pharmacology, neurophysiology, botany, biochemistry, organic chemistry. Relevant literature is found in many scattered sources, and is not easily accessible to the specialist in one field. No single abstracting service has heretofore been available that covers all the material of interest to psychopharmacologists.

Drugs change wave patterns.—Changes in brain wave patterns induced by administration of psychotropic drugs are both identifiable and measurable and may provide a useful approach to the understanding of the effects of drugs on the clinical state of psychiatric patients, an international panel of psychiatric researchers agreed at a conference supported by funds from the NIMH.

Recent years have seen a gradual increase in the sophisticated use of quantitative techniques of electroencephalography. Many investigators have been studying the effects of psychotropic drugs on the human electroencephalogram and have been noting significant changes.

Specific EEG changes can now be observed immediately following intravenous injection of psychotropic drugs or after several days of oral administration of these drugs, it was reported. Definite relationships between EEG changes and behavioral changes in psychiatric patients had been found by all investigators.

The participants agreed that all potent psychotropic drugs capable of producing behavioral changes also produce significant alterations in the electroencephalogram. It was suggested that electroencephalographic techniques might be useful for the characterization of newer psychotropic agents and might enable the clinical effects of such agents to be predicted successfully.

Drugs with differing behavioral effects were reported to show drug-specific EEG effects as well.

The panelists generally agreed that, while physiochemical brain changes are necessary for behavioral change, they are not in themselves sufficient to bring about and sustain improvement in the patient. Improvement also depends on the patient's personality and social environment.

Refinements in electronic instrumentation capable of measuring changes both in frequency and amplitude of brain waves have contributed significantly to this research advance. (Conference on Electroencephalography and Human Pharmacology, Third World Congress of Psychiatry.)

Persisting effects of reserpine.—Although reserpine is widely used in psychiatric and medical practice, the rates of recovery from the physiological effects of the drug have not been extensively delineated in man. NIMH grantees have recently studied the recovery curves of blood serotonin and pupil size as a measure of autonomic function in 14 female patients with chronic schizophrenia after single large doses of reserpine.

The results indicate that more than 5 weeks must be allowed after cessation of reserpine therapy in human beings for all drug effects to be considered absent. With a single dose of reserpine, blood serotonin had returned to normal in 5 weeks, and pupil size in 7 days. The action of a single large dose of reserpine seems to persist for 1 or 2 days in terms of bodily discomfort and tranquilization, 7 days in terms of miosis, and 4 or 5 weeks for blood serotonin values. Man, as compared with animals, seems markedly sensitive both to the blood and the central-nervous-system effects of reserpine. These findings underscore the importance of taking into account the interval between administration of reserpine and measurement of its effects in both clinical and laboratory studies.

(NIMH grantees Drs. Daniel X. Freedman and Arnold Benton, Yale University. Reported in New England Journal of Medicine.)

Studies on the neurophysiology of barbiturate addiction.—Chronic intoxication with barbiturates is in some respects a more serious kind of addiction than is addiction to opiates. Scientists have been handicapped in exploring the neurophysiological changes occurring in this condition by the difficulties of obtaining information on such changes in human subjects. A continuing series of studies at the NIMH Addiction Research Center, Lexington, Ky., has now disclosed that addiction to barbiturates can be induced in cats as well as in dogs. In both kinds of animals convulsions and bizarre behavior occur following withdrawal of barbital from chrnically intoxicated animals, just as it does in man, and makes possible investigation of neurophysiological changes during barbiturate intoxication. (Dr. Carl F. Essig, NIMH Addiction Research Center. Reported in Experimental Neurology.)

Short method of inducing experimental addiction to morphine in dogs.—In the past it has been necessary to administer morphine to dogs four times daily for weeks or months in order to produce physiological addiction, thus making investigations of the neurophysiological processes responsible for addiction difficult, time consuming, and expensive. Experiments in the Addiction Research Center during the year showed that it was possible to induce a measurable degree of addiction in dogs by administering a weak solution of morphine intravenously and continuously for an 8-hour period. This technique should greatly speed up the rate at which neurophysiological knowledge of addiction is accumulated. The technique may also be useful as a cheap and simple method of studying the addictiveness of newly developed pain-relieving drugs prior to trials of such drugs in patients. (Dr. William R. Martin, NIMH Addiction Research Center. Reported in Journal of Pharmacology and Experimental Therapeutics.)

Side effects of drugs.—A large proportion of somatic or physiological symptoms often reported as side effects from antidepressant medications were already present before treatment began, and therefore are not true side effects, grantees of the NIMH report.

The findings of a comparative study of somatic symptoms during pretreatment and treatment periods of patients on one of three antidepressant medications indicate that insufficient attention has been given to the pretreatment body complaints of depressed patients in reports of antidepressant drug studies.

Four groups from a total of 97 severely depressed hospitalized patients were treated with 3 different drugs. Physical complaints and observed clinical signs frequently reported as side effects were evaluated by the patient's ward physicians once in a 5-day pretreatment period and weekly during a 4–8 week treatment period.

Pretreatment incidence of somatic symptoms frequently attributed to drug factors during treatment was as high as 87 percent. The number of such quasi-side effects per patient increased as age increased, and was significantly higher in patients with psychotic depression. True side effects, somatic complaints that appeared only during treatment, were found less frequently than is usually reported, suggesting that reports of the high frequency of side effects reflect the presence of a substantial proportion of quasi-side effects. (NIMH grantee Bernard L. Busfield, Jr., Massachusetts Mental Health Center. Reported at American Psychiatric Association.)

Placebo effect in psychiatric drug research.—A study designed to measure placebo effect when no actual drugs were used and when not only patients but also the psychiatrists and nurses were unaware of the real nature of the study was conducted by NIMH grantees. Results indicated that, depending upon the observer and the method of evaluation, temporary improvement rates as high as 80 percent can be reported with placebo alone, a rate that compares favorably with that obtained in many enthusiastic uncontrolled studies of new drugs.

The simulated drug investigation involved 120 hospitalized psychiatric patients selected over a 1-year period from that part of the hospital population who were neither extremely depressed or agitated nor approaching convalescent status. Participating patients, psychiatrists, and nurses were told that a new tranquilizer and a new energizer were to be evaluated. Both "drugs" were actually placebos. Within the 2 groups of 60 patients, patients were assigned at random to either a "drug" or control group. Patients in both "drug" groups received no drug during a 2-week pretreatment and a 2-week posttreatment period, while during the intervening 6 weeks they received, if in the tranquilizer study, the "tranquilizer" placebo, and if in the energizer study, the "energizer" placebo. Patients in the control group received no somatotherapy during the 10-week study.

Observations concerning clinical improvement of the placebo group were made by doctors and nurses, and by the patients themselves. Depending on the group making the judgments, improvements due to placebo were noted to have occurred in from 53 percent to 80 percent of the patients during one or more of the weeks they were receiving the placebo. When evaluation included both placebo and control groups and objective rating procedures, the "tranquilizer placebo" showed only a slight advantage over the regular care (including psychotherapy) given, while the "energizer placebo" showed no advantage over such care.

Results of the study indicate that evaluations of uncontrolled drug studies are influenced by the expectations and suggestibilities of patient and staff, underscore the fact that in a good general milieu, acute patients tend to improve under routine treatment; and that general staff and administrative interest can sometimes increase apparent improvement. If these factors are not taken into account, unwarranted enthusiasm concerning a new drug may result. Nevertheless, many well-designed studies have demonstrated that tranquilizers and energizers now in clinical use are indeed more effective than hospital care plus placebo medicine.

(Drs. Armand W. Loranger, Curtis Prout and Mary Alice White, New York Hospital, White Plains, N.Y. Reported in Journal of American Medical Association.)

Psychobiological studies

Adrenocortical function and stress.—The study of factors that influence the production of metabolically important hormones during everyday activities has important implications for the understanding of psychosomatic relations as well as increased knowledge of many physical and mental disorders.

In continuing investigations of the relationship between adrenocortical function and the stress of everyday life, there is increasing evidence on endocrine systems having to do with bodily reaction to arousal and stress. Any major change in the life situation of an individual which is perceived by him as a personal threat is often accompanied by a change in the level of circulating adrenocortical hormones.

Recent studies of young adults living on the wards of the NIH Clinical Center have shown that certain psychosocial factors are related to modifications of hormonal elevation under stress. As the volunteers began their stay on the wards, they reacted to the change in their life situation with a marked elevation in corticosteroid levels on the first day of admission, with a drop by the end of the first week to a level that appeared to remain constant for the group over the course of their stay. However, there were variations in this basic pattern which were found to be a function of such psychosocial variables as general background and experience, immediate circumstances of the admission, and sex differences. Volunteers with a more sophisticated background in terms of type of college attended and experience in living in a variety of situations reacted to the transition with minimal disturbance, as reflected in hormonal levels. A group with college work problems reflected increased stress during the first week of admission, in contrast to the decrease shown by others. Sex differences in corticosteroid output were revealed in measures showing consistently higher levels but greater individual variability among young adult males than among females. Both sexes showed higher levels in corticosteroid output if the subjects were placed on mixed wards rather than isolated by sex. (Drs. Joseph H. Handlon, David Hamburg, NIMH, and John W. Mason, Walter Reed Army Medical Center. Reported at the American Psychological Association.)

Dreams and schizophrenics.—The discovery that dreaming is associated with specific patterns of brain waves and eye movements that can be recorded without disturbing sleep has provided a useful approach to studies of this phenomenon.

Findings that dreams are a universal experience and occupy an average of one-fifth of a sleeper's time (including those dreams not afterwards recalled) have raised the question of what biological function they serve. A project with schizophrenics was undertaken by an NIMH research team at St. Elizabeths Hospital, Washington, D.C., to investigate this question.

An individual deprived of the opportunity to dream develops psychological disturbances, such as anxiety, irritability, and inability to concentrate. Some investigations suggest that subjects who, over a period of several nights, are repeatedly awakened as soon as they start to dream, dream longer than usual when permitted to sleep undisturbed, as though trying to catch up.

If a definite amount of dreaming is necessary for everyone, the NIMH investigators asked, does the hallucinating schizophrenic, who might in a sense be said to be "dreaming" during his waking hours, dream less, or perhaps more, during the night? Preliminary findings from studies conducted on six schizophrenics who experienced hallucinations and a similar number who did not, indicated that schizophrenics who hallucinate, and those who do not, both dream while asleep and that the typical physiological pattern of their dreaming is not essentially different from that of normal persons.

The percentage of their time taken up with dreaming appears to be within the normal range and thus far no consistent differences have been noted in this respect between schizophrenics who experienced hallucinations and those who did not.

On the other hand, the tests showed striking differences in sleep patterns between the schizophrenic group as a whole, and normal subjects. First, the sleep of all the schizophrenics was very disturbed. Generally, this did not take the form of long periods of wakefulness. Most subjects went to sleep fairly promptly and slept until awakened next morning. But they seldom attained the depth of sleep of normal subjects, and their sleep was much more restless with more frequent body movements and brief awakenings. In contrast to the body movement pattern of normal subjects, the body movement of schizophrenics was particularly frequent during dream periods.

Most significant, the test subjects generally tended to awaken and remain awake a few minutes in the midst of their dream periods, something normal persons seldom do. Whether these preliminary results are characteristic of schizophrenics, or merely expressions of disturbed sleep that might be found in depressives and other severe anxiety states, requires further investigation. (Dr. Frederick Snyder, Dr. Irwin Feinberg, and Richard Koresko, NIMH. Reported at Conference on Sleep, EEG and Dreaming, University of Chicago.)

Response to auditory stimulation during sleep.—Studies on the physiology of sleep conducted by NIMH grantees indicate that the average sleeper responds indiscriminately to extraneous sounds. However, an individual motivated to awaken to a particular sound is awakened by that sound in all stages of sleep.

EEG recordings were made on 25 volunteers, 10 of whom had been motivated to awaken to specifically designated sounds. As the subjects reached various levels of sleep, a pretaped recording of familiar and unfamiliar sounds was played by a loudspeaker through the room.

Results showed that the EEG response to auditory stimulation decreased as the subjects fell into deeper sleep. The unmotivated subjects showed no discrimination as to the nature of the sound, responding to familiar and unfamiliar sound as noise per se. The previously motivated subjects, however, discriminated between types of sound in all stages of sleep, although in the deepest stage of sleep they woke more often to all stimuli. In lighter sleep, the discriminatory ability of the motivated subject was so specific that he was able to differentiate a telephone ring from bell ringing, door chimes, clock striking, and the like.

Sleep disturbances are of particular significance for individuals in pathologic depressed states. In view of the fact that the average individual does not discriminate familiar from unfamiliar sounds when he is awakened from sleep by sounds, these investigators suggest that the common complaint from depressed individuals regarding sleep disturbances may be based on a greater sensibility of such individuals to sound than that which the normal individual possesses in an equivalent stage of sleep. (NIMH grantees Dr. W. D. Wilson and associates, University of Texas Medical Branch. Reported in Archives of General Psychiatry.)

Sensory deprivation and behavioral abnormalities.—Grantees of NIMH have found that lesions induced in the lateral portion of the upper midbrain of the cat result in a consistent syndrome of symptoms that bears striking resemblance to the behavior of certain children who live in fantasy rather than reality (autistic children).

Little is known of the neurological or psychological basis of autism, although it has been regarded by some investigators as one form of early schizophrenia related to deprivation of normal emotional experiences during development. Children suffering from autism are very inattentive, may be unresponsive to many forms of sensory stimulation, and frequently walk or wander endlessly or engage in other highly repetitive, rhythmic activities from which it is almost impossible to distract them. Similar behavioral activities were observed in cats in whom the classical sensory pathways had been interrupted by lesions induced in the brain.

After creation of defects in the lateral brain stem, the cats were studied for 2½ years to detect changes in sensory capacities, affect or emotionality and in adaptive responses to the environment. They showed (1) marked sensory deficit characterized mainly by sensory inattention and poor localization in those modalities where direct pathways were interrupted, and also in vision and smell although no known direct pathways were interrupted; (2) lack of affect, muteness, and evidence of minimal autonomic responses; (3) hyperexploratory activity characterized by incessant stereotyped wandering, sniffing, and visual searching, as though hallucinating; and (4) exaggerated oral activities (snapping in response to tactile stimulation of lips, seizing and swallowing small objects even if inedible, overeating and holding objects too large to swallow firmly clamped in the mouth for long periods of time). Preoperative individual differences in behavior were largely eliminated. Although the animals were awake, active, and essentially normal in basic motor capacities, they appeared generally out of contact with the external sensory environment and their behavior seemed grossly inadequate in its adaptive value.

The scientists suggest that the syndrome observed in the cats may be due chiefly to the extensive, specific, sensory deprivation produced in the animals by interruption of the classical sensory pathways at the rostral midbrain. This research indicates that the patterned and localized sensory information carried to the forebrain via the lemnisci may be essential for normal behavior. Correlated with the effects of sensory isolation in man and sensory deprivation in animals as demonstrated by other investigators, the findings provide evidence of the importance of rich and varied sensory stimulation in the development and maintenance of attentive, affective, and adaptive behavior. (NIMH grantees Dr. J. M. Sprague and associates, University of Pennsylvania School of Medicine. Reported in Science.)

Learning deficits in environmentally restricted animals.—Two independent reports from NIMH grantees indicate that the observed limitation in intellectual achievement associated with restricted early environment is not permanent. Such learning limitations appear to be overcome by sufficient practice experience.

The investigations have shown that handled rats (those reared in an enriched environment) appeared to learn more rapidly than unhandled rats (those reared in a restricted environment) to find their way through a maze. However, after a long period of practice, the unhandled rats found their way through the maze with approximately the same speed as did the handled rats.

These experiments suggest that sufficient practice time is a critical factor in increasing the achievement levels of restricted animals; and that, with sufficient practice the low learning level generally associated with animals reared in a restricted environment tends to disappear. (Dr. Lewis Bernstein and Associates, University of Colorado. Reported in Journal of Psychosomatic Research.)

At the same time and working independently, other scientists investigated the possible basis for the reported lack of learning ability in animals reared in a restricted environment. They report that the restricted animals displayed a heightened exploratory drive by comparison with the animals reared in a free environment.

Two groups of rats, one reared under free and the other under restricted environmental conditions, were so motivated that their need to explore was blocked out. The results showed no significant differences between the learning performances of the two groups. These investigators conclude that the characteristically poor maze-solving performance generally observed among environmentally restricted rats may not be due to a deficiency in "intelligence" or maze-solving ability, but to an excessive need to explore (heightened exploratory drive), which temporarily blocks the problem-solving process.

The effects of restricted early experience have long been thought to result in a permanent "intellectual" deficit. These studies suggest that whatever deficit is observed may be due to a delay in learning caused by a need to explore the environment. Given sufficient practice to satisfy this need, the deficit apparently disappears. (Dr. P. J. Woods and Associates, Hollins College. Reported in Journal of Comparative and Physiological Psychology.)

Abnormal behavior of monkeys raised in isolation.—Recent investigations have shown that infant monkeys separated at birth from their mothers and having no physical contact with other monkeys developed abnormal behavior patterns. Some were detached, strangely mute, staring fixedly into space, and relatively indifferent to people and other monkeys. Others, when approached or even left alone, went into violent frenzies of rage, grasping and tearing at their legs with fury.

The animals raised under conditions of isolation showed extreme social abnormalities. Compared with monkeys born and raised under natural conditions, they showed infantile sexual behavior, absence of grooming, exaggerated aggression, and lack of friendly interaction and cooperation with each other. The observed differences were not due to the environmental difference between laboratory and "life in the wilds," but to lack of opportunity of these laboratory animals to develop social affectional patterns.

Those monkeys raised with "surrogate" mothers (forms of monkeys made of wire), who after long social training eventually produced young, became mothers who, in the words of the investigator, "having never known a real mother themselves became helpless, hopeless, heartless mothers devoid, or almost totally devoid, of any maternal feeling." (Dr. Harry Harlow, University of Wisconsin. Reported at American Psychological Association.)

Influence of group size on rat behavior.—A study of behavior patterns of an overpopulated colony of domesticated Norway rats revealed extreme disruption of normal behavior. Female rats in overcrowded pens built poor nests, scattered and deserted their young. Males exhibited several different types of disturbed behavior. "Territorial males" which protected a harem prevented other rats from entering the pens they inhabited. Other males were aggressive and fought with other rats although they had no territory to protect. Some rats became passive and slept all day, moving about only when the other inhabitants slept. A pathological need for proximity to others while eating was evident. This further intensified the overcrowding situation.

The investigator studied the problem of population density by dividing rats into 6 groups of about 80 each and confining them in pens built to accommodate only half that number. Overcrowding was intensified by the tendency of most rates to use only two of the four sections into which each pen was divided. (Dr. John B. Calhoun, NIHM, in press, Scientific American.)

PROGRESS IN TREATMENT

Mental hospital populations decline.—New developments in the public mental hospitals and in the communities served by the hospitals have, in the last few years, made it possible gradually to reduce the number of patients who must be maintained in a public hospital for a long period of time. These developments include: the increased availability of intensive treatment services within the hospital; the provision of additional community resources for dealing with the acute psychoses, and for providing aftercare for the newly discharged patient: and the more precise use of the psychopharmacological agents in relation to other, more traditional, therapies.

Despite a steadily increasing number of admissions, the number of persons resident in a public mental hospital on any one day has declined in the past 6 years. Data from the Institute's Biometrics Branch indicate that the 527,955 patients resident in the 287 public mental hospitals at the end of fiscal year 1961 represented a decrease of 7,314, or 1.4 percent, from the corresponding number at the end of fiscal year 1960. Since the end of fiscal 1955, the number of patients resident in these hospitals has declined by 5.6 percent. Between 1955 and 1961, the number of total admissions to public mental hospitals increased by 42.4 percent, with an increase between 1960 and 1961 of 7.8 percent. Net releases show an even greater—70.4 percent—increase since 1955, with an increase of 12.3 percent occurring between 1960 and 1961.

Psychiatric outpatient clinic services.—Rapid growth in psychiatric outpatient services throughout the United States during a recent 5-year period is indicated in data included in a nation-wide directory issued recently by the National Association for Mental Health in cooperation with NIMH. The directory provides basic information on over 1,400 outpatient psychiatric clinics.

An analysis of the data, gathered in 1959, indicates that such clinics have increased from 1,234 to 1,429, an increase of 16 percent, since publication of an earlier directory in 1954–55. The number of professional man-hours available in the clinics has increased by 41 percent to 265,000 hours per week.

The growth of clinic service both in terms of number of clinics and professional man-hours is almost nationwide. Forty-seven States reported increased man-hours between 1954–1955 and 1959; man-hours were doubled or more in seven States. For the Nation as a whole, the number of professional man-hours of service available per week for each estimated 100,000 population increased from 115 to 149. All but a few States show some improvement in this ratio.

The directory lists all regularly scheduled clinics in which a psychiatrist takes the medical responsibility for clinic patients. It also lists State and Federal hospitals for the mentally ill and for mental defectives, State mental health associations, State departments dealing with mental health, and all regional offices of HEW. (Outpatient Psychiatric Clinic Directory, published by National Association for Mental Health and NIMH, 1961.)

Statewide study of clinic outpatients.—The first comprehensive study of the characteristics of psychiatric outpatient clinics of an entire State, Maryland, has been carried out by a team of NIMH scientists and associates.

For the purposes of the study, a mental health clinic was defined as an administratively distinct psychiatric service for outpatients where a psychiatrist is in attendance at regularly scheduled hours and takes the medical responsibility for all the patients. Data were collected on the age, sex, color, place of residence, and mental disorder of every Maryland resident seen in such a clinic serving residents of the State during the year ending June 30, 1959.

The findings do not describe the distribution of mental disorders in various population groups but only of those receiving defined psychiatric services. Results indicate that less than one-half of 1 percent of the population are seen in a psychiatric clinic in a year.

It was found that, in more rural counties, clinic services primarily are for children, reflecting the use of the clinic by schoool psychological services and as a casework and court diagnostic facility in lieu of other community resources. All clinics reported long waiting lists for treatment of children, indicating marked inadequacy of services in all geographic areas. Clinic admission and termination rates were considerably higher for boys than girls.

Children under 5 and adults 65 and over have the lowest rates of admission to clinic; high rates for school children are followed by a decline in late adolescence, a secondary rise at ages 30 to 40 years was followed by another decline

The general decline in the clinic population past the age of 40 does not indicate diminishing disease with age, since it is accompanied by an increase in the rate of admission to inpatient care.

A lower psychiatric rate for adults was observed in less urbanized areas, which parallels earlier findings indicating that highest rates for hospitalization for schizophrenia occur in areas of high population mobility and density.

Other findings: In late adult life, brain syndromes associated with cerebral arteriosclerosis and senile or presenile brain disease predominate. Transient situational personality disorders (adjustment reaction) are of considerable numerical importance in childhood and decline at 18 years. In psychiatric classifications among children, personality disorders and mental deficiency were major problems; among adults, psychotic disorders led, followed by psychoneuroses.

Results of the survey, the investigators note, sharply point up the need for further intensive field studies along these lines, and demonstrate the usefulness to the psychiatrist, mental health program planner, sociologist and epidemiologist of such data obtained for an entire geographic area and referable to a population basis for computation of admission and termination rates. (Drs. Anita K. Bahn, Caroline Chandler, NIMH, and Leon Eisenberg, Johns Hopkins University. Reported in the American Journal of Psychiatry.)

Treatment techniques

Family group therapy.—A variety of approaches to family group therapy, a technique in which the patient and his family are treated as a group, have been reported during the year.

Its success as a method of dealing with the psychological problems of older children and their families is described in a Public Health monograph by one author who developed the approach as a means of treating disturbed adolescents, whose lack of response to the individual techniques successful with younger children and adults has posed a major problem in psychotherapy.

The method focuses on the family as a total entity, and is sociopsychological in orientation. Symptoms of family disturbance that have led the family to seek help are regarded as products of disruption in family interaction, most usually a breakdown in family communication, and not as the product of intrapsychic conflicts. During the weekly sessions the therapist's goal is to make the family conscious of the roles the various members play in relation to each other, and to demonstrate the family's essential unity and interdependence. (Dr. John E. Bell, NIMH consultant, region IX, USPHS. Reported in Public Health Monograph No. 64, Government Printing Office, 1961.)

Other studies in conjoint family therapy, conducted over a 5-year period at the Palo Alto Clinic in California have pointed up the usefulness of similar approaches in the treatment of schizophrenia. This project has also shown that exposure to this technique tends to change the therapeutic approach of the psychiatrist involved.

General goal of the weekly sessions is to alter the self-reinforcing mutually destructive networks of family interaction, and emphasis is given to influencing these patterns rather than examining their content. Responsibility for helpful participation is placed equally on all members of the family. As therapy proceeds, family messages are reinterpreted by the therapist, in a communicational rather than psychoanalytic sense; and advice may be given. The aim is not to tell the family members what to do, but to enable the defensive individuals to accept interest and help. In the family therapy situation, even therapists who have formerly worked with only one patient at a time quickly realize that the family is bound together in a mutually destructive way, and that the primary symptom presented by the group is a crippling entanglement which from the surface is apparent only to the patient.

As the program of family therapy has developed, modifications in traditional psychotherapeutic techniques have been made. The therapist has become more active; has shown more concern for altering behavior than for achieving "insight"; has focused on the present rather than on the past; and has emphasized attention to interaction rather than intrapersonal experience. (NIMH Grantees Drs. Don Jackson and John H. Weakland. Reported in Psychiatry.)

In another approach, the staff of the youth development project, a psychiatric outpatient clinic for adolescents at the University of Texas, has been conducting for 3 years a brief intensive family-centered psychotherapy program called multiple-impact therapy. In this procedure, family groups have been seen by an interdisciplinary team. Treatment includes extensive admissions procedures, 2 days of family and individual therapy, and followup.

Followup studies at 6 and 18 months on a series of 63 cases representative of a wide socioeconomic, cultural and diagnostic range indicate that the method does mobilize family self-rehabilitative processes and yields results comparable to other psychotherapies. Diagnostic phases appear especially suitable as a tool of clinical investigation. (NIMH Grantees Drs. Harold A. Goolishian and Eugene McDanald, University of Texas. Reported in A Multiple Impact Brief Psychotherapy Program.)

Preliminary evaluation of experiments conducted over a 4-year period at the NIMH Mental Health Study Center has revealed certain characteristics of the 60 families chosen for group therapy. Predominantly, they are families referred to the Center through their eldest child, who is in junior high school, is doing poor academically, disrupts the classroom, perhaps shows destructive behavior in the community, and who is in open warfare with his parents. The fact that 65 percent of the families came via their eldest child, and that school achievement problems were also represented in higher than expected proportions, suggests that the two phenomena may be part of the same process: the focusing by middle-class families on the achievement potential of their eldest children, as has recently been suggested by other investigators. (Drs. Robert S. Shellow, Bertram S. Brown and James W. Osberg, NIMH. Reported to American Orthopsychiatric Association.)

Comparative studies on psychotherapies.—Results of a 5-year followup study conducted by NIMH grantees on the effectiveness of various forms of psychotherapy disclose that long-term studies are not conclusive in evaluating the success of psychotherapy since life experiences tend to confound the effects of treatment. Instead, the investigators suggest, the relative success of psychotherapy should be measured by its more immediate results in reducing a patient's suffering and disability. The conclusion is based on findings that early observable differences in the effectiveness of different types of psychotherapy tend to disappear over a period of time.

The studies revealed that all types of psychotherapy produced two distinguishable but related effects: relief of distress, and improvement in social effectiveness. Improvement of distress, or relief of symptoms resulted primarily from the patient's expectation of help since it (1) occurred rapidly, (2) was independent of the particular type of therapy, (3) could be duplicated in some patients by administration of a placebo, and (4) persisted through the 5-year study period.

Improvement in personal functioning or social effectiveness could be distinguished from symptomatic relief because it (1) occurred more gradually (2) was related to the type of therapeutic experience, and (3) increased in time so that all patients showed on the average more improvement at the end of the 5-year period than after 6 months, regardless of type of therapy.

Especially noteworthy was the finding that differences in improvement in social effectiveness produced by the three forms of treatment which were apparent at 6 months had disappeared in 5 years. About two-thirds of the patients had improved symptomatically. The degree of improvement was found to be unrelated to the type of therapy but showed a relationship to the nature of the patient's complaints. The patients who improved most had relatively more psychological and fewer somatic complaints. (NIMH Grantee Jerome D. Frank and Associates, Johns Hopkins University Hospital. Reported to American Psychiatric Association.)

Alternatives to hospitalization.—Findings from a completed 3-year research project at Butler Health Center, Providence, R.I., suggest that many psychiatric patients who otherwise would need to be hospitalized full-time can be successfully treated without full-time hospitalization if an appropriate alternative treatment program can be provided. The decision of whether to hospitalize a patient or to provide another type of treatment program was made only after an intensive detailed analysis of the patient and his family by a multidisciplinary evaluation team. At Butler, it was seen that the evaluation process was as important as the treatment process.

The treatment phase at the Butler Center was likewise accompanied by refinements designed to show how a community mental health center can combine or extend its services to accommodate patients whose illnesses run the full gamut of psychiatric disorders. The Butler outpatient service worked in close cooperation with the Center's day service and inservice departments, thereby making it possible to transfer a patient from one service to another service if this was therapeutically desirable. This flexible arrangement made it possible to treat by alternative programs a group of 76 patients on outpatient basis who otherwise would have had to undergo full-time hospitalization. Contributing to the efficiency of the program was the fact that the members of the Butler evaluation team also served as the treatment team thereby keeping the patient in clear clinical focus at all times.

A significant fact about the 76 patients was that one-third were diagnosed as psychotic; yet the average duration of therapy required was 20.5 weeks for the group as a whole.

The findings point up the economy of alternative treatment programs when compared to the costs of full-term hospitalization. For patients of the same degree of illness, the cost for outpatient care was 41 percent less than for full-time care. These figures suggest that psychiatrically effective alternatives to residential treatment can reduce the economic burden of mental illness.

Chronic psychoses and recovery.—New insights into the nature of the conflicts experienced by chronic psychotics—and how they may be dealt with therapeutically—have also emerged from the Butler center study.

The findings indicate that the chronic psychotic suffers much less from the discord of competing emotions than do acute psychotics, but far more from an unrelenting anxiety of fixed intensity. In an attempt to neutralize and endure this anxiety the chronic psychotic develops defensive devices to achieve self-sufficiency and equanimity. In his view, the mental equilibrium thus achieved is easier to preserve than seeking gratification through interpersonal relationships.

Staff experiences with these patients and their families indicate that these psychopathological states have characteristics of their own and occur in definable family settings. Families of these patients show feelings of having special status or exclusiveness, accompanied by a pronounced tendency toward feuding, by great tenacity of purpose, and by strong feelings of failure and shame. Thus, in a sense, the chronic patient's illness can be perceived as a family feud fought largely at the level of psychological warfare.

To deal with these patients requires simultaneous therapeutic intervention at all levels of integration: (*a*) sociological, altering the social environment; (*b*) psychological, working with the patient in an intense personal way; and (*c*) physiological, utilizing drugs to alter the physiology of the patient. A fourth essential component of therapy is intensive work with the patient's family. An important consideration in therapeutic planning emerging from the study is that the nonprofessional attendant, rather than the highly trained professional, is often best suited to make initial contact with the chronic psychotic.

The results of the treatment the chronic psychotics received at Butler are encouraging. Of the 38 (out of 41) patients for whom followup data is available, only three were hospitalized and seven were attending the Butler day program when followup data was sought. The mean length of time in treatment (exclusive of outpatient treatment) was 12 months, ranging from 1 to 36 months; the mean length of time from discharge to followup was 18 months. At the time the project began, the mean number of years since the onset of psychosis, for the patients studied, was 8.5. (NIMH Grantees Drs. Robert W. Hyde, J. Sanbourne Rockoven and Richard H. York, Butler Health Center, Providence, R.I. Reported in Final Report on Butler Hospital Project.)

Pilot project for mental health counselors.—An NIMH pilot program to train mental health counselors for limited psychotherapy has produced preliminary findings indicating the feasibility of training carefully selected mature persons, without previous professional experience, for this type of work.

The project involved eight trainees working under close professional supervision with patients with emotional disorders.

The experiment was designed to determine whether such training might be used as a means of meeting the continuing manpower shortage for mental health personnel, and the need for low-cost therapy.

The project, begun in 1960, demonstrated that there is an untapped reservoir of psychotherapy manpower in the large group of intelligent married women around the age of 40, whose child-rearing responsibilities are over and who are looking for constructive activity outside the home.

The 8 trainees were selected from among 49 applicants. Median age was 40–44; all had children. All were college graduates; three had advanced degrees. Four had been psychoanalyzed. The group did practical work in individual and group therapy at NIH, participated in lectures and seminar discussions, did outside reading and report writing, and spent some time in community agencies (juveniel courts, clinics, a Federal probation office, a counseling center, and a social service agency.)

At the end of the first year, their performance, as judged on the basis of selected tape-recorded interviews from each trainee, was rated as satisfactory using as reference point an interview by a professional worker.

Success was also evaluated in regard to patient improvement. Of the 49 patients ranging in age from 15 to 55, who were seen by the trainees, 30 showed improvement ranging from slight to marked. None changed for the worse. None of the patients seen by each trainee on a once-a-week basis was regarded as very easy to treat. Sixty-nine percent were considered difficult or very difficult. The length of treatment, at the time evaluation was made, averaged 10 weeks. That the patients themselves were favorably impressed was demonstrated by the fact that of those who came asking for help, only one dropped out of therapy.

Supervisors in the community agencies in which the trainees were placed rated none of them less than satisfactory.

Supervising professionals involved in the project believe that after two semesters' work the trainees were prepared to perform useful therapeutic services as apprentices in settings such as clinics or university counseling centers where competent supervision could be provided and where ultimate responsibility for the patients was assumed by an experienced professional. The project is scheduled for 2 years' duration. (Drs. Margaret J. Rioch and Charmian Elkes, NIMH, and associates. Reported to Washington School of Psychiatry.)

CHILD AND FAMILY STUDIES

Early patterns of family living and social interaction are important factors in influencing individual development. Ways in which persons adjust to problems of living and cope with their environment are determined to considerable extent by behavioral patterns established during childhood and adolescence. NIMH investigators have been concerned with these patterns as they relate both to normal and abnormal behavior.

Effects of maternal employment on child rearing.—A mother's employment has little relation to her child-rearing characteristics, according to a recent NIMH study. However, child-rearing practices are significantly affected by mothers' fulfillment or frustration, in whatever role they play, and inferior mother-child relationships were found more generally among dissatisfied nonworking mothers.

One hundred mothers—50 working and 50 nonworking—were compared in the study following interviews in their homes. The subjects were from financially comfortable families in which the mother's income merely supplements the family budget. All the mothers were carefully matched in family, social and educational characteristics, a working husband was present, and there were from one to four children in each family.

Few differences in child-rearing practices appeared between mothers who worked and those who stayed at home. However, when mothers' motivations to work were considered (such as achieving certain valued family goals), those who preferred to work, but out of a sense of duty did not, appeared to have the greatest problems in dealing with their children. Child control was a continuing issue for 67 percent of these mothers, compared with 32 percent of the mothers who preferred not to work, 18 percent of the dissatisfied working mothers, and 42 percent of the satisfied working mothers.

More than half of the mothers worked as a means of supplementing family income to achieve cultural, status, educational, and health goals inaccessible without additional income. Forty-eight percent of this group stressed a need for self-fulfillment such as using their training, contributing to society, or being with people. Nonworking mothers refrained from work primarily because of a love of mothering (48 percent) ; a duty to mothering (36 percent) ; and a small group (15 percent) felt that it was an easier and freer life.

Analyses were also made of child-rearing differences associated with employment status among the mothers with high school and college training. Within the high-school group, maternal employment was associated with firmer child control, assignment of greater responsibility to children, and delegation of a stricter disciplinary role to the father. This difference between working and nonworking mothers did not appear within the college group.

On the other hand, the college working parents revealed a tendency to compensate for time away from their children by more planned shared activities with them than was found in the college nonworking group and the high-school working and nonworking groups.

The NIMH findings suggest that mothers' employment brings about varying child-rearing and familial adaptations depending on mothers' motivations, attitudes and cultural backgrounds. (Dr. Marian Radke Yarrow, NIMH. Reported in Children and at American Psychological Association.)

Children in nursery school.—The rationale for prevention of emotional disturbance that focuses on the mastery of a phase in early childhood development has been the subject of an NIMH research project. It is concerned neither with forestalling emotional disorders nor with building specific personality functions, but with reducing vulnerability to certain types of psychologic situations. The aim is to ensure that the child's experiences with developmental transitions or crises are mastery experiences rather than disorganizing failures.

As part of the program of the Biosocial Growth Center, a nursery school situation was designed to study and contribute to the mastery of three central issues confronting a group of 2½-year-old boys: their first geographic separation from home and mother ; a first opportunity for a close relationship with a substitute mother-figure; and an opportunity to attempt greater autonomy in creative and constructive play.

To foster mastery of the anxiety and confusion associated with separation from home and mother, meetings were held in the home with the family group, the parents visited the school prior to the beginning of the 4-week program, and the mothers were present during the first 2 days of school. In the first few days of total separation, when the child was picked up at home each morning by the teacher, extra care was taken to deal supportively with the early stages of separation panic.

Five forms of mastery can be described from the reactions of the first 40 boys to the structured home-separation experience. The modal form—immediate effective experiencing of the newness as a potential threat followed by rapid, effective, pleasureful mastery—included approximately 50 percent of the boys: the remainder evidenced mild defensive reaction, severe defensive reaction, panic reaction, or nonengagement. With the first mastery form, nothing in the way of preventive actions was required beyond the provision of opportunity for the child's dormant capacities to grow and adapt. For those children showing degrees of defensive reaction or panic, special supportive measures were planned to meet the needs of the child and often other members of his family.

The children in the "nonengagement" group, who showed inadequate affective contact with the new developmental issues and stereotyped, repetitive behavior patterns, were apparently slow developers or possibly mentally retarded. The fact that they were included in the study despite a careful history for developmental defect and regular physical check-ups illustrates the difficulty of identifying a child's readiness for psychologic growth without actually exposing him to the situation of newness.

It is suggested that preventive action programs could be begun, even at the present state of knowledge, by using the mastery forms as guideposts to action. (Dr. D. Wells Goodrich, NIMH, published in Prevention of Mental Disorders in Children, Basic Books, July 1961.)

Transition from high school to college.—Studies of a group of college-bound high school seniors by NIMH investigators have provided useful clues to predict the success with which the students will adapt to the new college experience. It is anticipated that the results of this and similar studies will provide psychiatrists with answers that will help students who suffer from emotional disturbances during their freshman year.

The pilot study involved 20 competent college-bound volunteers of both sexes from a Maryland high school. The sample was selected from a group of volunteers on the basis of academic standing and social adjustment.

The students maintained confidence in their ability to meet the requirements of the new situation by: (1) referring to past accomplishment of similar situations; (2) regarding college as a gradual part of the continuous process of maturation; (3) exhibiting an anticipatory detachment from parents and some peer relationships; (4) acquiring advance information about the new situation, thus reducing its ambiguity; (5) "role rehearsal" or enacting in advance various forms of behavior which they associated generally with college students and adults (most of them felt that their summer job experience confirmed an individual self-image adequate to cope with problems in the adult world); (6) identifying themselves as part of a high school group sharing a reputation for being well-prepared for college; and (7) viewing college as a potentially friendly and supportive environment.

The college experience was not approached without some anxiety, but the students displayed an impressive ability during the transition period to manage stress. Mechanisms for coping with anxiety included: (1) acceptance of anxiety as something shared by their peers; (2) an attitude that worry had a useful function; and (3) a rehearsal in fantasy of their future behavior.

The study on the transition from high school to college is one of a series of projects which includes investigation of a group of emotionally disturbed college freshmen. Comparison between characteristics of the successful students with those suffering breakdowns in their freshman year is expected to provide data that will help in detecting attitudes and self-concepts that make late adolescents vulnerable to emotional disturbance under transitional stress. (Dr. Earle Silber and associates, NIMH, reported to American Psychological Association.)

New psychological test development.—NIMH investigators have developed a student thematic apperception test (STAT) for measuring the adaptive and problem-solving potential of college freshmen. Results of early tests given to three groups of college freshmen indicate that this psychological test may be useful in predicting whether adolescents are likely to be able to cope successfully with the transition to college, or may be vulnerable to breakdown.

The test consists of a set of 11 picture slides of typical college scenes and situations which tend to be new and problematic to freshmen. The students are instructed to create an imaginative story about each picture and to describe the circumstances leading up to the situation; next, to tell what is going on, including the thoughts and feelings of the characters involved; and finally, what the outcome will be.

The test was administered initially to 30 students, representing three groups: 10 students who showed exceptional competence in social and academic adaptation in high school; 10 patients who were hospitalized for emotional difficulties during their college freshman year; and 10 university freshmen selected from an English class who had passed at the 85 percentile level on an advanced placement test.

Considerable group differences were noted in responses as to solution, activity of the hero, and favorableness of resolution by which the stories were rated. Comparison of the overall ratings reveal that both of the normal groups had a substantially higher frequency of positive ratings than the patient group. In general, the patient group (1) showed considerably lower problem-solving competence than the other two groups; (2) produced few clear solutions in potentially stressful college situations; and (3) expended proportionately greater efforts, only to achieve unfavorable solutions.

Further systematic evaluations of the test are currently underway to determine its predictive and discriminative potential for assessing the coping behavior of students. Results achieved thus far suggest that this test can be useful in predicting vulnerability among adolescents prior to their freshman year at college. (Drs. George Coelho and Earle Silber, NIMH. Reported to American Psychological Association.)

Family influence in schizophrenic thought disorder.—NIMH investigations of schizophrenic illness in terms of thought disorder, the "fragmentation of the thinking process" described by Bleuler in 1911, have shown that the presence and variety of schizophrenic illness in an individual can be predicted from the form of thinking in the rest of the family in which the patient has developed.

Family therapy studies and extensive psychological testing were undertaken with the parents, the late adolescent or young adult hospitalized patient, and any brothers or sisters living in the family household. For comparison purposes, disturbed but nonschizophrenic patients and their families were also seen and tested. Verbatim test protocols from family members other than the patient were then sent to a predicting psychologist who had received no clinical or test data on the patients themselves.

On the basis of a three-level diagnostic grouping, frankly schizophrenic, frankly nonschizophrenic, and borderline, the psychologist predicted characteristics of the patient member of the family compared with clinical observations as follows: Of 13 patients clinically diagnosed as frankly schizophrenic, 12 were predicted to be frankly schizophrenic from the test protocols of the rest of the family and 1 was predicted to be a borderline schizophrenic. Of four patients clinically regarded as borderline, four were predicted to be borderline schizophrenics. Of three patients clinically regarded as disturbed but nonschizophrenic, one was predicted to be nonschizophrenic, and two to be possibly borderline. The psychologist then used the tests to predict the severity of the patient's illness, again with remarkable accuracy compared with the clinical diagnosis. In the second phase of the procedure, the psychologist was given test protocols from the patients themselves, identified by code number only and with extraneous clues to a family relationship deleted, and asked to "blind" match the patients with their families. Of 18 families, 16 were matched correctly with the patient-member.

Another finding is that the family constellation as a whole, rather than the characteristics of individual members, is a determining factor in the development of schizophrenic disturbance. A higher order of predictive accuracy was achieved by taking the family social organization into account than by predictions based on individual parental characteristics, including individual parental thought disorder. The latter finding seems more compatible with an evironmentally determined rather than a gene-determined interpretation of schizophrenic thought disorder. (Drs. Lyman C. Wynne and Margaret Thaler Singer, NIMH. Reported at Cincinnati Society of Neurology and Psychiatry.)

A cross-cultural study of community behavior settings.—A cross-cultural study of American and English community behavior settings involving the participation of both children and adults sharply delineates basic differences in approach to child-rearing practices and goals in the two countries.

A comparison was made of children's regimens in a town in Kansas ("Midwest") with those in a similar town in Yorkshire, England ("Yoredale") by studying community behavior units such as sports, music, and dramatic programs, paper routes, etc., where adults and children are involved together, both as participants and as audience. This method made it possible to measure the functioning of children in their environment, rather than any particular aspect of their behavior. They found that 22 percent of Midwest's community behavior settings that carry power and responsibility are dependent to an important degree upon the involvement of children and adolescents, compared with 9 percent in Yoredale. Of Midwest's sports settings, involving adults and children, 83 percent are completely dependent upon child and adolescent contestants; this holds for only 25 percent of Yoredale's. Further, 85 percent of concerts and programs attended by adults involve child and adolescent participation in Midwest, compared with 12 percent in Yoredale.

These findings reflect fundamental differences in child-rearing practices and goals. American parents believe the earlier a child learns to take the difficulties, failures, decisions, and tensions as well as the achievements and satisfactions in a real-life situation, the better adult he will become. They are therefore interested in the all-round child, the adjustable child, the one who is willing to do his part even when he cannot do it very well. In contrast, English parents believe that slow preparation removed from the main areas of adult living is best for children and constitutes wholesome behavior. As a result, their children have fewer positive and negative experiences that are viewed by adults; and are therefore less concerned with self-regard, social status, self-analysis, and uncertainty in relation to these adults. (NIMH Grantee Dr. Roger Barker and Associates, University of Kansas, in a chapter in Studying Personality Cross-Culturally, Row, Peterson & Co., 1961.)

SPECIAL AREAS

With the growing complexity of society, certain specific problem areas such as juvenile delinquency, aging, mental retardation, alcoholism, drug addiction, and suicide have assumed increased proportions. Because of the relevance of such problems to the field of mental health and illness, the Institute shares with many other groups a continuing concern in them, and seeks to initiate and coordinate research programs that will provide better understanding of contributing factors and, hopefully, will also provide clues pointing toward ways in which they can be alleviated.

Predictability of juvenile delinquency sought.—A "mathematical yardstick" to measure the usefulness of public housing and other projects in reducing juvenile delinquency is being sought by New York University, N.Y. The study, which is being supported by an NIMH grant, is trying to work out an expected rate of delinquency for each of the city's 2,000 neighborhoods, based on 45 social and economic factors. This is then being measured against the actual rate of delinquency based on an analysis of 70,000 cases of youngsters up to the age of 20 who were brought to the courts in 1950, 1957, and 1960.

Investigators have focused on factors including (1) family disorganization—number of married persons living without spouses, and number of working women; (2) socioeconomic squalor—number of families with incomes under $2,000, number of individuals with unskilled occupations, number of overcrowded dwellings; (3) socio-economic contrast—range of incomes and educational background; (4) density of population—number of youths as against adults.

The study is attempting to find answers to such questions as whether slum clearance projects reduce the expected rate of delinquency; and, if so, if only because so-called "better families" are admitted. In this connection, the study will seek answers, for example, as to whether delinquency increases or decreases in border zones surrounding housing projects. (NIMH Grantee Dr. Isidor Chein, New York University. Reported at New York Chapter, American Statistical Association.)

Psychiatric clinic at a jail.—A psychiatric clinic for youthful offenders (aged 16 to 25) was established in 1958 in the New Haven County jail by the Connecticut State Department of Mental Health. The primary function of the clinic was to develop a treatment program that would be effective in such a setting and which could be established in other jails. Youthful offenders, 85 in number, confined between November 1, 1958 and June 15, 1959 (41 percent Negro, 59 percent white), had all been arrested for minor crimes and had received short sentences of less than a year and a half; 63 percent had been in jail before. Of the total, 70 percent were sufficiently mentally ill so that a phychiatric diagnosis could be established; eight youths were in need of either institutional or other protective care. Nearly 90 percent of those with multiple jail records displayed manifest psychiatric problems, in contrast to only 40 percent of the first offenders. Repeaters exhibited a high prevalence of antisocial reaction; first offenders included a larger percentage of schizophrenics and mental defectives.

Evaluation of the effectiveness of the clinic indicates that the jail clinic shows more promise for definitive treatment for first offenders, who tend to be acute cases and lend themselves to some degree of therapy. The clinic shows less promise as a treatment center for chronic offenders, although careful diagnostic evaluation and planning for treatment after release might be carried out in the clinic for this group. The discovery of seven schizophrenics and two mental defectives would appear to justify in itself the psychiatric screening of youthful offenders. (NIMH Grantees Nathaniel London and Jerome Myers, Yale University. Reported in Archives of General Psychiatry.)

Study of views on successful aging.—The first detailed profile of the attitudes of "middle age" and "old age" toward aging has resulted from the Kansas City Study of Adult Life, supported by the NIMH.

The research, initiated in 1950, began as a cross-sectional survey of adults 40–70 years old and has since broadened into a full scale social-psychological investigation of aging in which a panel of older adults, aged 40–85, is interviewed twice yearly. It has been found that "successful aging" can be measured by means of a "Life Satisfaction Rating" which measures such attitudes as confidence, optimism, pleasure from everyday activities, satisfaction that life goals have been achieved, and a view that life is meaningful. The investigators found that "inner satisfaction" indicated by these attitudes was not related to age or sex, but was somewhat related to socioeconomic status and definitely related to marital status. They concluded that, given reasonable health and financial security, advanced age does not necessarily bring with it decreased satisfaction with life. Further, they found there is no one pattern of successful aging because of the diversity existing among older as well as younger people with regard to social and psychological patterns that accompany satisfaction with life.

Another investigator has proposed that the crucial test of "successful" aging is retirement—a crisis period which, if passed through successfully, will be one in which an individual does one or more of the following: decreases energy expenditure; revises the activity budget, spends more time in nonwork roles; has more leisure time; and increases time spent in contemplation.

In another aspect of the Kansas City study, subjects were separated into four social classes—upper middle, lower middle, upper lower, and lower lower—and were asked emotionally charged questions about growing old. In general it was found that the upper class man envisions a slow period of arriving at maturiy, followed by a relatively short period defined as "old age"—a time for relaxation, leisure, security, and partial withdrawal. The lower class man, on the other hand, sees life speeded up—the first phases of adulthood appear to pass quickly, followed by a long period of "old age," which is viewed in terms of decline, physical weakening, and slowing down. For women, the Kansas City study bears out the same trend—moving down the social ladder, aging seems to occur earlier. (NIMH Grantees Drs. Robert D. Hess, Robert J. Havighurst, William E. Henry, Bernice L. Neugarten, University of Chicago. Reported in University of Chicago Reports.)

Aging and productivity.—Age has little to do with productivity among employable personnel, according to a study designed to determine the exent of differences in productivity between older and younger employees.

Conducted at the University of Chicago Industrial Relations Center under a grant from the NIMH, the study also aimed at determining whether objective measures of aging could take the place of chronological age as a determinant of retirement. Findings by a team representing medicine, biology, psychology, sociology, and economics indicated that "certain older employees are able to maintain, under existing work practices, and with incentive stimulation, a level of productivity equal to that of workers 20 years younger." Although they could offer no ready explanation for this finding, the investigators ruled out the common belief that output declines with age. They emphasized that although the 166 production workers examined in the study varied in their ability to produce, the variations were not tied to chronological age.

Following physical examinations, it was reported that the majority of the workers were physiologically able to continue working past the age of 65. In other aspects of the research, the investigators concluded that arteries in the eye deteriorate markedly with age, that psychomotor performance falls off significantly with age, that mental reserve abilities favor the younger group. An interesting finding was that job attitudes and motivations differ sharply between the older and younger men, with most of the younger men wishing to retire by age 65, and the older men who did not think of themselves as old and who were attached to their jobs wishing to continue working after age 65. (NIMH Grantee Dr. Ward Halstead and Associates, University of Chicago; Drs. Robert Kleemeier, Washington University, and Leonard Z. Breen, Purdue University. Reported in University of Chicago Reports.)

Performance speed measured in aging.—An apparatus designed and constructed at the NIMH—the psychomet—has yielded significant data on the extent to which aging results in a general slowing of mental and behavioral processes.

By requiring the subject to press keys in response to various simple and complex stimuli shown on a panel of 10 lights, the psychomet objectively and scientifically measures speed of reaction in an unusually broad range of tasks. In the young, speed depends more on the nature of the specific task performed and is not necessarily consistent with speed of performance of other tasks. In older individuals, however, there is a general slowing of psychomotor performance.

Because of the relevance of these findings to the assessment of psycho-physiological changes in the normal adult, the Federal Aviation Agency has used the psychomet in aging studies on civil air pilots and air traffic controllers. The Agency has completed examinations of 160 individuals and the results are being analyzed in cooperation with the Section on Aging and the Biometrics Branch, NIMH. Preliminary results indicate statistically significant age trends toward slowing of performance and the surprising finding that trends are appearing in relatively young healthy men. FAA investigators have also found psychomotor speed deficits in relatively mild stable cardiac cases.

Further data analysis and research will explore possible physiological bases for the changes. Of considerable importance is the suspicion that observable behavioral changes may antecede later-to-appear physiological changes related to health. These findings pose implications for determining the extent to which behavioral changes of advancing age may predict length of life and disease states, and may eventually have a place in early detection methods in health surveys.

Having demonstrated that slowing of behavior in the aging is measurable, broad, and important psychologically, it is now possible to explore more hopefully the mechanism of aging in the central nervous system and behavior, particularly with regard to the higher cognitive processes. (Dr. James E. Birren, NIMH, and Associates. In press, Gerontologia.)

Rutgers Center of Alcohol Studies.—A grant from the NIMH has made possible the relocation at Rutgers State University, New Brunswick, N.J., of the center of alcohol studies, which had its beginnings at Yale University in 1921.

The principal function of the center will include:

(1) Research into various social, biological, psychological and sociological aspects of alcohol.

(2) Teaching of groups with special interests in problems of alcohol, such as clergymen, public health officers, personnel workers, police, social workers and nurses. This will be done in a summer program, the Yale counterpart of which has been nationally famous for years.

(3) Documentation of all forms of study dealing with alcohol.

(4) Publication and dissemination of information, including the Quarterly Journal of Studies on Alcohol.

The new center of alcohol studies will be a unit within the graduate school at the university.

Thyroid therapy for acute alcoholic stupor.—NIMH grantees have found that the intravenous injection of a solution prepared from sodium triiodothyronine powder is effective in bringing a patient out of a stuporous or semicomatose condition within one-fourth the usual time, if the condition is secondary to acute alcoholism. A rational medical history can then be obtained and a differential diagnosis made, where necessary.

The only side reaction observed was moderate tremulousness and nervousness in a number of patients, 6 to 8 hours after the injection. Since these reactions occurred at a time when the blood alcohol had dropped precipitously from its initial value, however, it is likely that such reactions are secondary to a state of rapid alcohol withdrawal rather than to the administered hormone.

Twenty patients, the majority of whom were chronic alcoholics, were selected at random from patients admitted to the alcoholic ward and divided into two groups, experimental and control. All treated patients in the study received the same dose of sodium triiodothyronine powder. Chemical determinations of blood alcohol concentration were made in both groups at stated intervals. Criteria for evaluation of the hormone were: (1) Decline in blood alcohol; (2) ability to give a rational history, walk a straight line, hold arms and fingers outstretched without noticeable tremor; and (3) disappearance of odor of alcohol from the breath as estimated by several observers.

A comparison of the patients who received this treatment and the untreated acutely intoxicated controls showed the following results: The rate of blood alcohol declined twice as rapidly in the treated patients as in the controls; the treated patients were judged to be clinically sober and able to give a rational medical history within 2 hours after the injection; the odor of alcohol was undetected on the breath 2 hours after treatment although it persisted for 6 to 10 hours in the untreated controls.

The studies indicate that intravenous therapy appears to be a valuable adjunct in the treatment of acute alcoholism, particularly when the patient is admitted to the hospital in a stuporous or semicomatose state. It is theorized that the observed acceleration of alcohol metabolism may be the result of a direct effect of the hormone on the hepatic enzyme systems that convert alcohol to acetaldehyde, in addition to a general enhancement of body metabolism. (NIMH grantee Dr. Marshall Goldberg and associates, St. Vincent's Hospital, Worcester, Mass. Reported in New England journal of Medicine.)

Detection of problem drinkers among industrial employees.—Previously unsuspected alcoholics in an industrial concern may be detected by their psychological test performances and work maladjustments, an NIMH-supported study reveals.

Preliminary findings indicate several signs by which alcoholics may be detected and distinguished from other problem employees. These include: high scores on psychological screening tests designed to detect suspected alcoholics; below-average work performance ratings by supervisors; and signs of job maladjustment, including multiple absences of less than 4 days, high accident rates, and interpersonal difficulties.

The study also revealed that the number of medical clinical visits for alcoholics exceeded that for nonproblem employees, but was less than that for other types of problem employees, suggesting the difficulty of detection by this method.

Using self-administered screening tests, casework interviews with employees, and reviews of company personnel records, the investigators found techniques which show promise for revealing problem drinking in any moderately sized company, particularly if a trained personnel specialist cooperates with an industrial physician in their application.

The study further suggested that an exploratory, nonpressing discussion with suspected alcoholics coupled with a firm company-union policy are essential steps in a remedial approach to the problem of alcoholism among industrial employees. (NIMH grantee Dr. W. Donald Ross, University of Cincinnati. Reported to Ohio Psychiatry Association.)

National Conference on Alcohol and Traffic Safety.—A National Conference on Alcohol and Traffic Safety sponsored by the NIMH and the Division of Accident Prevention, HEW, was held on May 21–24, 1961, in Pittsburgh, Pa. Approximately 170 specialists from the fields of medicine, law, psychology, physiology, and sociology attended.

One of the major functions of the meeting was to provide a forum for the exchange of ideas on the drinking-driving problem. This was accomplished through the formal presentation of papers and through several discussion group sessions.

Visiting scientists from England, Australia, Sweden, and Canada participated in the conference. They presented material reflecting the historical concern with the problem in their respective countries and indicated the nature and direction of research designed to aid in handling the problem.

Seven major papers were presented and covered problem areas such as the social-cultural factors that predispose toward drinking before driving, the psychological and physiological effects of alcohol on the organism with special reference to driving behavior, the adequacy and inadequacy of drinking-driving mortality and morbidity statistics, the difficulties in enforcement and prosecution, and educational and mass motivational aspects of prevention.

Drug addiction

Vulnerability to addiction among social deviants.—Recent NIMH studies indicate that alcoholics and narcotic addicts are generally social deviants prior to addiction. Some but not all are aggressive and antisocial; many are merely inept and inadequate. In the United States social deviance must be measured with respect to the customs and institutions of the dominant middle class which determines, with respect to the law at least, acceptability or unacceptability of particular actions or behavior.

The first of several powerful interacting factors that determine the vulnerability of the deviant to initial addiction appears to be that the social patterns conducive to deviant behavior are found most frequently in the areas where opiates are relatively available. The same conditions that produce the deviant also produce more ready access to opiates, and with regard to opiates and alcohol provide a greater degree of exposure to persons who are addicted.

Secondly, a lack of social controls appears to determine the deviant's willingness to experiment with drugs as well as other forms of unusual behavior. Descriptions of nondeliquent, nonaddicted adolescents and their families in deprived areas suggest that familial discipline and variety of interests and activities act as deterrents to addiction and other deviant behavior. The degree of individual deviance is perhaps determined by the family inculcation of preferences and inhibitions held in common by the larger society.

The social deviant is deficient in the self-critical, counteranxiety, guilt reactions that might deter him from unusual behavior. Teenage addicts studies said there was no "good" reason for them to stop using drugs except that they found the habit expensive and sometimes became ill.

Besides being deficient in social controls, the deviant seems to prefer short-term satisfactions to long-term gains, and does not get as much satisfaction or reinforcement from daily pursuits as does the teen-age non-delinquent living in the same neighborhood. With fewer social deterrents to drug use and fewer satisfying daily pursuits, drug-produced euphoria is more acceptable to the deviant.

Many narcotic addicts state their initial trial of opiates was extremely pleasant and some said they first used narcotics to ease alcoholic abstinence symptoms. Others maintained their first experience was very unpleasant but that repeated trials made the effects highly desirable.

Acceptability to the deviant himself of deviant models and of unusual forms of behavior including use of drugs appears to be the most critical element in addiction in the United States. The study suggests that the immature, inadequate deviant who has not found independence in solving problems of adult life may find temporary independence from frustration, conflict, anxiety and monotony in alcohol, or nearly complete dissolution of such difficulties in opiates. (Dr. Harris E. Hill, NIMH Addiction Research Center, Lexington, Ky., Reported in the Quarterly Journal of Studies on Alcohol.)

Mental retardation

Epidemiology of mental retardation.—Seven hundred and twenty-four mentally defective patients admitted to a State hospital between 1948 and 1952 were studied by NIMH grantees. The results of the study demonstrate that characteristics of the patient and his family, and the patient's social interactions with his environment, are related to age of admission, diagnosis, sex, IQ, socio-economic status, and ethnic origin. These latter variables are also interrelated. Physical handicaps were found to be more common in patients admitted at an early age who are severely defective. In general, newly admitted patients appear divisible into two groups. First, one that enters the hospital at an early age with a severe degree of mental deficiency that has organic components, including superimposed physical handicaps and certain behavioral manifestations. The social, economic, and cultural backgrounds of these patients are similar to those of the general population. The second group is represented by those admitted in the adolescent years: their deficiency is usually mild: superimposed physical handicaps are uncommon; and "acting-out" behavior is frequently noted. Their socio-economic backgrounds are different from those of the general population (e.g., a significant number of the parents represent the lower occupational and educational strata.) The findings of this study indicate that, in the absence of adequate background information, age and IQ may be used to predict with a reasonable degree of accuracy the other patient characteristics. (NIMH Grantee George Tarjan and associates, Pacific State Hospital, Pomona, Calif. Reported in American Journal of Disturbed Children.)

Frequency of types of cretinism.—Sporadic cretinism includes two classes: athyroid and goiterous cretinism. Among the latter, at least three biochemical defects have been described. The relative frequency of each type of cretinism, however, has been unknown. Research has been conducted by NIMH grantees utilizing a new technique for estimating the relative frequency of each type. The present study provides biochemical data obtained in a comprehensive study of a large series of cretins located in the Michigan area. A total of 80 cretins was found in the surveyed population, 56 of whom were studied: 38 cretins had no definite evidence of a thyroid gland at any time during the study, and 41 were born after the introduction of iodized salt into Michigan. The minimum incidence of thyroid glands in cretins was found to be 21 percent.

Inability of the thyroid gland to organically bind iodine was detected by discharge of I^{131} (net radioactive iodine) after administration of potassium thiocyanate (*KSCN) to six patients, and chromatography of the thyroid gland hydrolysates in four patients. Inability to bind iodine was the most common clearly identifiable defect in these cretins with thyroid glands.

The familial incidence of cretinism was higher in subjects with thyroid glands than in subjects without thyroid glands. Cretins with thyroid glands were found in families with athryotic cretins. Serial studies indicate that progressive postnatal failure of thyroid function may result in cretinism. (NIMH Grantee Dr. William H. Beierwaltes and associates, Reported in Pediatrics.)

Suicide

Suicide research advanced by prevention center.—Suicide continues to occupy a significant role as a public health problem, ranking 10th among causes of death within the United States each year.

The Suicide Prevention Center in Los Angeles, Calif., supported by a 5-year NIMH project grant has, in addition to its clinical activities, been carrying on a number of research studies of both theoretical and practical nature.

The center has conducted several surveys of various aspects of suicide in Los Angeles County and is currently engaged in two others. One survey determined that the ratio of attempts to commit suicide in a large-scale community like Los Angeles, to those that actually succeed, was conservatively 8 to 1. The modal picture of the suicide attempt is: (*a*) female; (*b*) Caucasian; (*c*) probably in her twenties; (*d*) married or single; (*e*) a housewife; (*f*) native born; (*g*) attempting by barbiturates; (*h*) giving as reason marital difficulties or depression; and (*i*) living in an apartment house area. The modal suicide committer is likely to be: (*a*) male; (*b*) Caucasian; (*c*) in his forties or older; (*d*) married; (*e*) a skilled or unskilled worker; (*f*) native born; (*g*) committing suicide by gun, hanging, or carbon monoxide poisoning; (*h*) giving as a reason ill health, depression, or marital difficulties; and (*i*) living in an apartment house area.

A study examined the psychological characteristics of genuine suicide notes from different socioeconomic areas of Los Angeles County. Findings indicated that the emotions expressed by suicidal persons will vary more or less consistently within socioeconomic areas, and the patterns for expression of these emotions will reflect the nature of the social class position of which the victims are members. People apparently commit suicide in different ways; that is with expression or denial of affection; with mention or avoidance of specific reasons, some of which are definitely related to the socioeconomic level to which they belong.

An important problem area developed by the Suicide Prevention Center has been the investigation of equivocal cases of suicide. When the medical examiner-coroner of Los Angeles County has cases which he feels are questionable in certification of mode of death (the most frequent being determination between suicide and accident) he requests the staff of the Suicide Prevention Center to investigate them. This is done by collection of information which will allow the evaluation of the psychological aspects, the psychiatric status, the personality, organization and suicidal intent of the deceased. Thus, the case history, personality traits, interpersonal relationships, communication channels, etc., help provide a complete picture of the individual from which his suicidal intention can be derived.

The Center has derived several checklists for evaluation of suicidal potentiality. One checklist is used for emergency assessment and allows the worker to gather critical information in a minimum of time. Some items on this emergency checklist are: prior suicidal behavior; loss of loved person; diagnostic impression; communication aspects; medical symptoms; resources available; and reaction of informants. This list is expanded when there is much information and time available to include items such as intrapersonal aspects, in which conscious and unconscious intention and ego organization is noted, and interpersonal aspects, in which communication and environmental aspects are evaluated.

Intensive investigations of patients in neuropsychiatric and general medical and surgical hospitals are comparing those who have committed suicide with similar groups of patients (controls) who have not. These groups include schizophrenic patients; patients with terminal illness; depressive reactions; anxiety reactions; respiratory illnesses, and others. (Edward S. Shneidman and Norman L. Farberow, in Cry for Help, McGraw-Hill Publishing Co., 1961.)

Communications and information problems in mental health.—Communications and information problems in the mental health field have been investigated for the past 6 years by a research team of the Institute of Communications Research, University of Illinois. The research, supported by a series of special grants from the NIMH, was carried out in two phases: first, the investigators measured the opinions and attitudes of the public and specialists in the mental health field and analyzed the mental health content of the mass media; second, they studied methods for effecting changes of public attitudes and opinions.

Among the results of the project were these findings—

> The average man is not misinformed about mental health; rather he is uninformed.
>
> Not only laymen but also general medical practitioners tend to regard the mentally ill as dangerous, unintelligent, and unpredictable.
>
> The mass media convey ideas about mental health that are less correct than those held by the public at large.
>
> The public lacks a usable, nontechnical vocabulary with which to discuss mental health concepts.

The investigators suggest that information communicated to the public will promote favorable attitudes toward mental health concepts if (1) the concepts are visible in the message (directly mentioned) or associated with visible concepts (generalization), (2) the message has a high interest value, (3) the message is thought to come from an authoritative source (e.g., a university or a psychiatrist), and (4) the message makes the reader feel secure by sounding certain, by providing solutions, by presenting an understandable explanation, and by reducing anxiety in other ways. (Jum C. Nunnally, Jr., Charles E. Osgood, and Wilbur Schramm, University of Illinois, in Popular Conceptions of Mental Health, Holt, Rinehart, and Winston, Inc., 1961.)

Attitudes toward the mentally ill.—Current attitudes toward the mentally ill have been summarized as a sequency of denial, isolation and rejection, and it has been postulated that these attitudes were immutable. Using some of the same questions employed in previous attitude studies conducted by Drs. John and Elaine Cummings and Shirley Star, NIMH grantees at Johns Hopkins University directed the interviewing of a probability sample of the Baltimore city population.

In spite of the fact that this was a low-income, poorly educated populaiton—presumed to be less knowledgeable and sophisticated than most—the results of the survey differed significantly from those of previous studies.

The sample was not particularly rejective of the mentally ill, nor was there much empirical support for the concept of a popular belief in the isolation of the mentally ill. As a result of the survey, the authors offer alternative hypotheses to current theories of attitudes toward the mentally ill. These are: (1) it is possible that educational materials in mental hygiene do indeed produce changes in public attitude; (2) that the alleged stigma attached to mental illness has been overstated or is concentrated in selcted segments of the population; (3) that popular attitudes toward the mentally ill are much like attitudes toward victims of other illnesses, and except in special instances the mentally ill are not regarded as exhibiting deviant behavior. (Drs. Paul V. Lemkau and Guido M. Crocetti, Johns Hopkins University. Reported to American Psychiatric Association.)

NATIONAL HEART INSTITUTE

FRIDAY, FEBRUARY 9, 1962.

WITNESSES

DR. RALPH E. KNUTTI, DIRECTOR, NATIONAL HEART INSTITUTE
DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
RICHARD E. SEGGEL, EXECUTIVE OFFICER
DR. LUTHER L. TERRY, SURGEON GENERAL
JAMES F. KELLY, DEPARTMENT BUDGET OFFICER

Object classification

[In thousands of dollars]

		1961 actual	1962 estimate	1963 estimate
11	Personnel compensation:			
	Permanent positions	4,992	5,938	6,839
	Positions other than permanent	73	154	123
	Other personnel compensation	61	53	60
	Total personnel compensation	5,126	6,145	7,022
12	Personnel benefits	611	835	979
21	Travel and transportation of persons	383	748	851
22	Transportation of things	87	111	100
23	Rent, communications, and utilities	95	135	153
24	Printing and reproduction	16	40	47
25	Other services	1,022	1,875	1,549
	Payment to—			
	"National Institutes of Health management fund".	4,128	5,073	5,641
	"Bureau of State Services management fund"	59	136	137
26	Supplies and materials	683	839	1,019
31	Equipment	295	645	529
32	Lands and structures	------------	620	380
41	Grants, subsidies, and contributions	73,488	95,190	108,874
	Subtotal	85,993	112,392	127,281
	Deduct quarters and subsistence charges	3	3	3
	Total obligations	85,990	112,389	127,278

Personnel summary

	1961 actual	1962 estimate	1963 estimate
Total number of permanent positions	837	1,020	1,108
Full-time equivalent of other positions	15	27	23
Average number of all employees	742	903	1,021
Number of employees at end of year	772	1,055	1,169
Average GS grade	7.1	7.4	7.5
Average GS salary	$6,367	$6,473	$6,536

Program and financing

[In thousands of dollars]

	1961 actual	1962 estimate	1963 estimate
Program by activities:			
1. Grants and related contracts:			
(*a*) Research	55,418	76,036	89,720
(*b*) Fellowships	2,800	3,615	3,615
(*c*) Training	11,970	10,539	10,539
(*d*) State control programs	3,300	5,000	5,000
Total, grants and related contracts	73,488	95,190	108,874
2. Direct operations:			
(*a*) Research	7,780	9,342	9,985
(*b*) Collaborative studies	993	903	1,330
(*c*) Training activities	190	186	186
(*d*) Professional and technical assistance	2,578	3,985	4,111
(*e*) Review and approval of grants	1,225	1,674	1,958
(*f*) Administration	262	432	454
(*g*) Gerontology building		620	380
Total, direct operations	13,028	17,142	18,404
Total program costs [1]	86,516	112,332	127,278
Change in selected resources [2]	−526	57	
Total obligations	85,990	112,389	127,278
Financing:			
Comparative transfers to other accounts	249	500	
Unobligated balance brought forward			−380
Unobligated balance carried forward		380	
Unobligated balance lapsing	661	19,595	
New obligational authority	86,900	132,864	126,898
New obligational authority:			
Appropriation	86,900	132,912	126,898
Transferred to "Operating expenses, Public Buildings Service," General Services Administration (75 Stat. 353)		−48	
Appropriation (adjusted)	86,900	132,864	126,898

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[1] Includes capital outlay as follows: 1961, $295,000; 1962, $645,000; 1963, $529,000.

[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1960, $720,000 (1961 adjustments, −$17,000); 1961, $177,000; 1962, $234,000; 1963, $234,000.

Mr. FOGARTY. Dr. Knutti, we are pleased to have you with us this afternoon. This is your first appearance before this committee.

BIOGRAPHICAL SKETCH OF DR. KNUTTI

Will you give us some of your background for the purpose of the record?

Dr. KNUTTI. I will be glad to, Mr. Fogarty.

I was born in California, educated in West Virginia, through college, and graduated with my M.D. degree from Yale Medical School.

I was an assistant in pathology at Vanderbilt University, and I had then an internship in surgery at Western Reserve in Cleveland. I spent 2 years as an assistant in pathology and bacteriology at the Rockefeller Institute for Medical Research in New York City.

I then went to the University of Rochester, New York, first as instructor, and finally assistant professor of pathology. From there, I went to the University of Southern California, where I was associate professor of pathology and director of laboratories of the Los Angeles Children's Hospital.

I joined the commissioned corps of the Public Health Service in 1951 and until last fall, when I assumed my present position, I had been in charge of the extramural programs of the National Institute of Arthritis and Metabolic Diseases.

General Statement

Mr. Fogarty. All right; do you have a statement for the committee?

Dr. Knutti. Yes, sir.

Mr. Fogarty. You may summarize it, or read it all, whatever you want to do.

Dr. Knutti. All right, sir. I have a short summary of my opening statement I will read, with your permission.

Mr. Fogarty. All right. We will file the other one at this point.

(The prepared statement of Dr. Knutti follows:)

Statement by Director, National Heart Institute, Public Health Service, on National Heart Institute

Mr. Chairman and members of the committee, the year's activities in the mounting attack upon heart disease reflect both substantive research advances and the beginning of new bases for program developments that will bring maximum gains in reducing the vast toll of heart deaths and disabilities. The support of research and training and the provision of aid to the States for their community programs through this year's appropriations to the National Heart Institute are adding a strengthened tempo to the fight against the Nation's leading cause of death.

This statement is an assessment of activities in terms of the components of the Institute's program, with attention to developments in areas of especial interest and opportunity. The review is designed to provide the Congress a summary discussion of value in its consideration of current and proposed National Heart Institute activities.

In such a consideration, the signficance to health and the economy of the problem being attacked is, of course, a paramount factor. Although heart disease has come to be known as the leading killer, the sheer size, the costs, and the effects of this complex of illness of the heart and blood vessels are sometimes lost sight of. A brief report upon the human and economics costs of heart disease, therefore, is useful in establishing perspective for the National Heart Intitute's program.

MAGNITUDE OF HEART DISEASE PROBLEM

Several striking facts illustrate the magnitude and nature of the problem of heart disease and the significance of its effects in death, disability, and economic burdens.

Every minute at least one person dies from heart disease somewhere in the United States, and more than half of all the deaths each year are caused by heart disease.

More Americans are killed by heart disease in 4 months than were slain in all 4 years of World War II.

Heart disease strikes heavily at all age groups, not merely among older people. One-third of all heart deaths are in persons under age 65.

Heart disease afflicts over 10 million persons. Over half of them are in their most productive years—ages 25 to 64.

Military manpower losses from heart disease are severe. Over 3 percent of all World War II selective service registrants were rejected for heart disease; and its pecentage of rejectees for military service continues high to the present. About 80,000 men were discharged because of heart disease—or died of it in service—in 1942–45.

Each year, in industry alone, about 338 million man-days are estimated lost because of heart disease; and the cost in lost productivity of people in the total labor force disabled by heart disease, while incalculable precisely, is estimated to run toward billions of dollars.

Although the rate at which heart disease strikes is decreasing slightly, the number of deaths each year is moving upward, toward the 1 million mark. In 1951 the number of cardiovascular deaths was 764,281. Last year, over 900,000 died from heart disease.

NEW DEVELOPMENTS

Summarizing advances in the strengthening of current programs and in the implementation of new resources, it may be said that the year's activities are characterized by the effects of the need for sound, long-range planning and a widened range of multidisciplinary and interinstitutional collaboration and cooperation.

Progress was made along a number of fronts in developing program activities of especial opportunity for heart research and therefore of particular interest to the Congress.

Heart program projects (centers)

Coordinated with the general National Institutes of Health program for noncategorical research centers, this new resource in the cardiovascular field is a logical component of the overall approach supported by the Congress for providing a new dimension in medical research, meeting institutional and national needs.

In the heart program projects and centers field, the current fiscal year to date has seen the awarding of nine grants. Thus, with 18 grants awarded for heart research centers in the past fiscal year, and 9 to date this year there are now some 27 current awards, representing a sound start upon this important new program.

An example of a typical program supported by a heart grant shows how it is enabling the development of a new cardiovascular clinical research resource. The grantee institution has developed a 10-research bed component, which will increase to 20 beds in the second year. The grant is also making possible new facilities for investigation of intensive patient care and complex X-ray and other instrumentation, which will permit new approaches involving coordinated research work between such departments as cardiology, X-ray, and surgery in the hospital. Ancillary aspects of the research program will involve psychobiological, epidemiological, and basic science disciplines. The heart program project (center) grant, therefore, is adding a whole new dimension in research at the Institution.

Primate resources

The primate research center program of the National Heart Institute was launched in 1960 with the award of grants to the Medical Research Foundation of Oregon for the construction, at Portland, of the first regional primate center. In 1961, the second year of the program, construction and operation grants have been awarded for two additional regional primate centers—one at the University of Washington in Seattle and one at the University of Wisconsin in Madison. It also appears that initiation of two or three other regional centers—in the Northeast and South—will be included in the 1962 fiscal year program as it develops further. (A special report containing background and fuller detail on the primate program has been prepared for the committee on developments to date.)

Diet and heart disease

Increasing research evidence that the kind and amount of fat in the diet can influence and alter the blood levels of cholesterol and other fatty substances has stimulated general interest in the role dietary fat may play in relation to atherosclerosis and coronary disease. It has not been conclusively demonstrated, however, that lowering of blood cholesterol levels by changing usual dietary habits of fat consumption will reduce the risk of heart attacks. More data from research will be necessary to fill gaps in our knowledge. Careful consideration and planning continues for a long-term study, in large population samples, which may be required to establish the relationship between dietary fat and susceptibility to atherosclerosis and coronary heart disease. Several applications for grants to determine the actual feasibility of such a study—which would necessitate marked changes in dietary patterns—are under discussion. Whether a large-scale population study can be successfully and practicably undertaken and supported is a question that must await the results of such preliminary feasibility studies.

Epidemiology and biometrics

The Heart Institute is expanding its work in epidemiology and biometrics and has strengthened its organization devoted to this area. A new staff unit has been established which is comprised of the Biometrics Research Branch, the Field Epidemiological Research Section, the Framingham Epidemiology Section, and the Geographic Pathology Section.

Data accumulated in epidemiology studies are pinpointing pertinent factors related to the development and progression of coronary heart disease. It has become apparent that, because of such findings, susceptibility to coronary disease can now be determined to some degree. The expectation also seems warranted that, as continuing studies provide a better description of the factors involved, this knowledge may lead to eventual development of preventive measures through attempts to change alterable factors when present.

Gerontology research facility

Last year there was explicit recognition by the Congress of the need for developing the potential of the Institute's gerontological research operation and the opportunity for growth of this research in collaboration with the Baltimore community, where the operation has been underway for a number of years. This recognition was expressed by the Congress in indicating that a new gerontological facility was needed and in providing funds for the planning of such a facility to be located on the grounds of the Baltimore city hospitals, where the present operation has been carried on in limited space made available by the city. Negotiations and discussions are progressing toward planning the facility through utilization of funds available for the purpose. The building location is to be made available to the Government for the development of the program as a strong resource for a broad and varied multidisciplinary research attack on cardiovascular and other aging problems of significance.

Scientific communication

The Institute continued to devote attention to efforts for the increase and improvement of scientific information communication. One activity of import is the endeavor of the National Library of Medicine to develop an electronic machine system for information documentation, storage, and retrieval. The National Heart Institute has continued its collaboration and assistance in this project.

Training

The National Heart Institute is currently supporting approximately 320 undergraduate and gratuate training programs to meet the dual objectives of: (1) Improving the quality of both basic and clinical research training in fields concerned with the study, prevention, and treatment of cardiovascular disease; and (2) attracting promising young students or investigators to careers in medical research in order to increase the national supply of cariovascular scientists, teachers, and highly trained physicians.

SUBSTANTIVE PROGRESS

Progress during the year in the substance of heart research—the discoveries of new knowledge—was considerable, both in findings made in basic fields, such as physiology, and in research additions to knowledge useful for more immediate application, such as new or improved drugs.

A sense of some of the specific accomplishments of the scientific work conducted and supported by the National Heart Institute is provided by the "Highlights of Heart Research," submitted with this statement.

In addition to these highlights of research of the year, the following sections, reviewing in broader terms the research work conducted or supported by the Institute, also reveal the forward march of scientific investigations in the cardiovascular field.

HEART INSTITUTE RESEARCH

The research conducted by the National Heart Institute places major emphasis upon basic cardiovascular investigations. These studies seek new knowledge about the structure, function, and abnormalities of the cardiovascular system. Closely associated with these studies are those concerned with the application of fundamental knowledge to the diagnosis, prevention, and treatment of diseases of the heart and blood vessels. Some Heart Institute research in these two areas are described below.

Atherosclerosis

Cholesterol has continued as the prime suspect in the development of atherosclerosis, with the amounts and kinds of fat consumed playing an important supporting role. However, eating fats is only the first link in an exceedingly complex chain of events in the development of atherosclerosis. The deposition of cholesterol and other fatty substances in the blood vessel wall is one of the last links in the chain. It is probable that the answer to the riddle posed by atherosclerosis is to be found somewhere between, in the complicated processes of fat metabolism.

Cholesterol.—A series of studies by NHI scientists has defined the probable sequence of steps involved in cholesterol synthesis and has identified the intermediate products evolved during the integration of 2-carbon acetate units into the 27-carbon cholesterol molecule. Basic knowledge of this sort is especially vital in view of the current surge of interest in drugs that reduce serum cholesterol levels by interfering with its synthesis by the body.

This approach is beset by a number of formidable problems, one of the most serious being to determine which, if any, of the many biochemical steps in cholesterol synthesis can be blocked safely. Many of the intermediate compounds evolved in cholesterol synthesis are also needed for the synthesis of other substances vital to the body. Cholesterol itself has functions other than clogging up blood vessels: it is a precursor in the synthesis of bile acids and many important hormones.

MER–29 (Triparanol, Merrell), a drug that has been intensively studied by NHI scientists, had apparently avoided the precursor problem only to run head on into another. The drug blocks what is probably the last step in cholesterol synthesis: the conversion of desmosterol to cholesterol. The NHI scientists noted that the fall in serum cholesterol produced by MER–29 was accompanied by a rise in serum desmosterol, a compound identical to cholesterol except for two missing hydrogen atoms.

Virtually nothing was known about the metabolism of desmosterol, since it is found in significant quantities only after treatment with MER–29. Its close structural similarity to cholesterol made the scientists suspect that desmosterol would also exhibit similar biochemical behavior in the body.

Subsequent studies have confirmed this suspicion. Desmosterol readily substitutes for cholesterol in the synthesis of bile acids and hormones. Unfortunately, it also appears to substitute just as readily for cholesterol in the formation of atherosclerotic lesions in animals.

Fatty acids.—The chief repository of fatty acids is the body's adipose tissue. During periods of plenty, such as immediately after meals, fatty acids absorbed from the circulatiton or synthesized by adipose tissue from other substances are converted to triglycerides for storage. These triglycerides can be broken down and their fatty acids released to supply metabolic fuels during periods of fasting or when increased activity or emergencies impose increased energy demands on the body.

Actually, triglycerides synthesis and triglycerides breakdown go on continuously in adipose tissue. It is the relative rates of these two processes that appear to be the primary factors determining whether there will be a net uptake or a net release of lipid by adipose tisssue. Thus the body may regulate its serum lipid levels through nerve, hormonal, or other mechanisms that affect either or both of these processes.

Recent NHI studies suggest that one of the most important of these regulatory factors may be glucose, which appears to be essential to triglyceride synthesis by adipose tissue. Without glucose, adipose tissue cannot replace the triglycerides constantly being withdrawn from its reserves.

These studies help to explain why fatty acids are mobilized in large quantities during periods of fasting, but hardly at all immediately after meals. For some time after meals, enough circulating glucose is available to adipose tissue to support a brisk rate of triglyceride synthesis. This process preempts most of the fatty acids derived from the breakdown of triglycerides and also encourages the uptake of circulating lipid.

Later on, however, the levels of circulating glucose fall. As less and less glucose becomes available to adipose tissue, its rate of triglyceride synthesis falls off. Eventually triglycerides are being broken down faster than they are being formed. The free fatty acid pool in adipose tissue increases, discouraging further lipid uptake and eventually "overflowing" into the circulation.

The release of free fatty acids is also subject to nerve and hormonal controls. The large-scale mobilization of fatty acids in response to vigorous exercise or stress appears to involve the interplay of the pituitary, the adrenal glands, and the autonomic (involuntary) nervous system.

Earlier NHI studies had shown that the pituitary hormone ACTH played an important role in the mobilization of depot lipid that occurred in animals subjected to such stresses as pain or prolonged exposure to cold. These studies also indicated that ACTH did not act directly, but rather by triggering the release of cortisone and perhaps other fat-mobilizing hormones from the adrenal cortex. However, a surprising finding was that the stress-induced fat mobilization, which has appeared to be an all-hormone show, could be prevented by drugs that blocked the action of norepinephrine at sympathetic nerve endings.

Norepinephrine is a neurohormone stored at sympathetic nerve terminals. It is released by nerve impulses to transmit their messages to target organs. Among these target organs are the fat cells of adipose tissue, which contains significant quantities of norepinephrine.

The NHI studies indicate that norepinephrine is essential to the fat-releasing action of ACTH and its hormonal mediators, and that the autonomic nervous system exercises its share of control over fat mobilization primarily by regulating the availability of norepinephrine in adipose tissue. The studies suggest that when stress or increased activity sharply increase the body's energy needs, more norepinephrine is released in adipose tissue by stepped-up sympathetic activity. The supply might be augmented by norepinephrine and epinephrine released from the adrenal medulla and arriving in adipose tissue via the blood. ACTH and its mediators, also released in larger amounts under such circumstances, then act in concert with norepinephrine to bring about the large-scale mobilization of depot lipid.

Hypertension

Amines are nitrogen-containing compounds derived from the amino acids of dietary protein. A number of these substances are potent stimulants and blood vessel constrictors, and several are suspected of being intimately involved in the still-mysterious mechanisms by which the body regulates its blood pressure.

One member of this family of compounds, norepinephrine, is of particular interest because it appears to be the key to the action of many drugs currently used to treat hypertension. Most of these drugs lower blood pressure by preventing sympathetic nerve impulses calling for blood vessel constriction from making their wishes known to the muscles of the blood vessel wall. They do so by interfering with the action of norepinephrine, the chemical agent that conducts nerve impulse traffic between sympathetic terminals and their target organs.

Alpha-methyl DOPA (Merck, Sharp & Dohme), a new drug that has continued to show great promise against hypertension in NHI clinical trials, appears to act by blocking the storage sites of norepinephrine at these nerve terminals. As a result, the norepinephrine normally held in reserve at the terminals is liberated to diffuse away or to be set upon and destroyed by enzymes. A similar fate awaits much of the norepinephrine subsequently formed there. Eventually, this steady drain depletes the terminal area of so much of its norepinephrine that nerve impulse transmission is impeded.

Alpha-methyl DOPA belongs to a family of compounds that first aroused clinical interest because of their ability to inhibit the enzyme decarboxylase. Since decarboxylase is essential to the production of norepinephrine, serotonin, and other biologically important amines, drug-induced blockade of this enzyme appeared to offer a promising new approach to the treatment of hypertension.

As it turned out, the clinical successes scored against hypertension by alpha-methyl DOPA were not related at all to its ability to inhibit decarboxylase. A number of its relatives also inhibit this enzyme, but have no effect whatever on blood pressure.

Enzyme inhibition does appear to be the key to the blood pressure effects of MO–911 (Abbott), another promising antihypertensive drug being clinically tested by NHI scientists. This drug inhibits monoamine oxidase (MAO), an enzyme that inactivates norepinephrine, serotonin, and other amines. The ability of such drugs to lower blood pressure is related to their ability to inhibit this enzyme, but nobody yet knows why.

MO–911 thus far appears to be largely free from the toxicity that had characterized earlier MAO inhibitors. The severe side effects produced by these earlier drugs had precluded their use as therapeutic agents against hypertension and had aroused skepticism that MAO inhibition was a sound approach to the problem.

It now appears that the toxicity of the earlier inhibitors was due to their chemical derivation from hydrazine, a highly toxic compound that can cause damage to the brain and other tissues. MO–911 is not a hydrazine derivative, and appears to combine high potency as an MAO inhibitor with low toxicity.

Another finding by NHI scientists that might bear importantly on hypertension concerns a heretofore unsuspected role played by norepinephrine at sympathetic ganglia. Here, the studies indicate, norepinephrine may exert a "braking" action to hold wide fluctuations in central sympathetic output within biologically tolerable limits. It appears to do so by "damping" the action of acetylcholine, a chemical transmitter whose role in nerve-to-nerve transmission at these ganglia resembles that of norepinephrine at sympathetic nerve endings.

The studies suggest that both norepinephrine and acetylcholine are released by nerve impulses at these nerve junctions. Acetylcholine acts as the transmitter for the incoming impulses, but its action is buffered by norepinephrine to hold the strength of the outgoing impulses within carefully prescribed limits.

The findings suggest that this and similar buffer mechanisms may be an important means by which the body maintains a tight rein on the activity of its nervous system. If so, a defect in such mechanisms might be a factor worth considering as a possible cause of some forms of hypertension, and drugs that selectively interact with such mechanisms worth considering as possible means of treatment.

Congestive heart failure

A number of regulatory mechanisms operate to modify heart output in accordance with the shifting circulatory demands of the body. They assist the heart in meeting its circulatory obligations primarily by affecting heart rate and/or heart output per pumping stroke. When hypertension or other factors increase the energy toll levied on the heart in meeting these demands, certain of these mechanisms may enable the heart to compensate for a time by increasing its pumping efficiency. Eventually, however, the demands may become so exorbitant that the heart can no longer meet them and goes into failure.

NHI studies have shown that the vigor with which the heart receiving chambers (atria) contract is an important factor affecting heart output. A vigorous, efficient atrial contraction pumps more blood into the ventricle and also increases its pumping efficiency in accordance with Starling's law. By emptying the atria more completely, it also leaves in its wake a lower pressure to be overcome by the venous feed lines supplying blood to the heart. These studies also suggest that failure of the atrial "booster pump" may be an important factor in the development of congestive heart failure.

"Starling's law" explains the heart's response to varying circulatory loads in terms of changes in heart filling pressure. While continuously operative, this law is also continuously subject to amendment by other control mechanisms. One of the most important of these is the carotid sinus, a specialized receptor which reacts to changes in carotid artery pressure by initiating nervous reflexes to compensate for those changes.

Earlier NHI studies had shown that carotid sinus reflexes could affect heart output by directly increasing or decreasing the efficiency of the atrial "booster pump." Subsequent studies have shown that carotid reflexes also affect heart performance by constricting or dilating the venous bed, which, in turn, affects heart filling pressure.

Carotid sinus reflexes may also affect the distribution of blood to the body's organ systems. Carotid reflexes causing blood vessel constriction raise blood pressure in the affected vessels but may actually decrease flow through those vessels. However, NHI studies have shown that, in those parts of the body where increased metabolic activity increases their need for blood, local tissue demands take precedence and can override carotid reflexes calling for blood vessel constriction. The blood channels to these areas remain dilated, transporting larger volumes of blood, thanks to the general increase in pressure produced by blood vessel constriction elsewhere.

The catechol amines, norepinephrine and its near relative epinephrine, can also modify Starling's law by (1) causing the heart muscle fibers to contract more forcefully from any given heart filling pressure and fiber length, and (2) increasing the overall efficiency of heart muscle contraction by affecting the timing of events in the cardiac cycle.

NHI studies have shown that the heart readily takes up and stores catechol amines from the blood. This uptake, which is aided by an active transport mechanism, may be an important means by which the heart recharges its sympathetic terminals. The high volume of flow through the heart causes catechol amines released by sympathetic stimulation to be washed out rapidly; thus some sort of replenishment mechanism is needed to keep the sympathetic nerve mechanisms so important to heart performers always "at the ready."

Aldosterone.—A hormone from the adrenal cortex, aldosterone is released in response to salt depletion, acute blood loss, and other factors that reduce blood volume or pressure. By promoting salt and water retention, aldosterone acts secondarily to maintain or expand blood volume. Excessive quantities of aldosterone are frequently secreted in congestive heart failure, and contribute to the edema attending this disorder.

Earlier NHI studies had shown that the stimulus to aldosterone production and secretion was provided by another hormone, and that this hormone was produced by the kidney. Subsequent studies have provided strong evidence that this aldosterone-stimulating hormone is renin, which is released by the kidney in response to a fall in renal artery pressure and flow. Renin does not act directly, but gives rise to angiotensin II, which in turn stimulates the production and secretion of aldosterone by the adrenal cortex.

Surgery

Cardiac shunts can result from a number of congenital heart defects, and are one of the most frequently encountered symptoms of congenital heart disease. A cardiac shunt is the flow of blood between the normally separate right and left sides of the heart through abnormal openings in the muscular wall that divides the heart into two pumping systems. Most of the congenital defects causing left-to-right shunts can be corrected by surgery. The risk is low and the results usually excellent if the shunt is diagnosed and corrected before irreversible heart and pulmonary damage has occurred.

Precordial scanning, a technique developed elsewhere, has been modified and improved by NHI scientists to provide a simple, safe, and sensitive means of detecting the presence of left-to-right shunts. The modified technique does not require catheterization or the withdrawal of blood samples, involves no risk and very little discomfort to the patient, and can usually be done in 10 minutes or less. These features make it an excellent technique for screening patients suspected of having such shunts and for evaluating the results of surgery to correct them.

The precordial scanning technique has also been adapted by NHI scientists to detect acquired defects of the aortic and mitral valves and to measure heart output. All of these procedures require cardiac catheterization, however.

The transseptal catheterization technique was developed several years ago by NHI scientists to provide safe access to the left heart chambers for diagnostic purposes. The technique involves passing a catheter into the right atrium. A hollow needle is then passed up the catheter and used to puncture the muscular wall (septum) between the right and left atria. A second catheter is then passed through the needle into the left side of the heart.

Since its development, the transseptal technique has proved its worth in over 450 cases. Minor modifications have been made in the original technique to increase its safety and its usefulness in diagnosis.

RESEARCH GRANTS

The research grants program of the National Heart Institute supports heart disease research in over 300 universities and hospitals all over the country. More than 2,000 separate research projects are underway. The following summaries represent only a few of the hundreds of findings reported in the scientific literature during the year.

Atherosclerosis

Serum cholesterol levels are considered one of the most reliable indicators of relative susceptibility to atherosclerosis. However, NHI grantees have found that, over the course of a year, serum cholesterol levels exhibit a striking pattern of seasonal variation in healthy young males. Serum cholesterol levels rose sharply in November, remained on a high plateau through January, then declined gradually, reaching lowest values for the year during spring and summer. The seasonal variation appeared to occur independently of such factors as diet, physical activity, or psychic stress. The grantees suggest that, whatever its cause, this variation is a factor to be considered when evaluating the significance of serum cholesterol levels in experimental or clinical situations.

Serum cholesterol levels can be reduced by thyroid hormones, but the doses needed to maintain low serum cholesterol also increase basal metabolic rate and may cause angina pain in heart patients. Several synthetic analogs, near relatives of thyroxine, appear able to hold serum cholesterol down without elevating basal metabolism in patients with normal thyroid function.

Chickens who were fed at periodic mealtimes were found to develop serum cholesterol levels twice as high and atherosclerosis seven times as severe as did chickens allowed free access to food 24 hours a day. This occurred even though the meal-eating chickens consumed less of the same kind of food. Meal eating also slowed the regression of atherosclerosis previously induced in these chickens.

A comparison of four diets fed to infants during their first 6 to 8 weeks of life showed that the diet whose fat calories were derived mainly from butterfat produced higher serum levels of total lipid and cholesterol than did the other three, whose fat calories were derived from vegetable or mixed sources and which contained 20 to 30 times as much of the unsaturated fatty acid linoleic acid.

Coronary heart disease

In the past, surgical procedures for treating severe coronary heart disease have sought to improve the heart's collateral circulation rather than risk a direct surgical attack on the blocked vessels themselves. However, the safety and clinical effectiveness of surgery to remove clots and lesions obstructing coronary vessels has been increased thanks to improved techniques for accurately locating such obstructions and to improved surgical techniques that reduce the risk of constriction of small vessels at the site of surgical incision. NHI grantees report that their results have been encouraging enough to recommend this direct surgical approach in carefully selected patients with intractable angina pectoris.

Some investigators have maintained that nitroglycerine and other nitrates relieve angina pain by dilating the coronary arteries and improving blood flow to the heart, others that nitrates act by reducing the workload of the heart to a level more commensurate with its blood supply. The latter hypothesis is supported by grantee studies showing that, in coronary patients, nitrates did not alter coronary artery flow, but reduced coronary artery resistance, heart output, and systemic blood pressure.

Hypertension

Some forms of hypertension result from kidney disease or from lesions obstructing blood flow to the kidney. The kidney reacts to an inadequate blood supply by releasing renin, which gives rise to angiotensin II, a potent blood vessel constrictor. Hypertension of renal origin can frequently be cured by removing or bypassing obstructions blocking renal artery flow; or, if only one kidney is involved, by removing the diseased kidney. Evaluating the diagnostic and prognostic value of various techniques in current use, NHI grantees report that greatest accuracy was obtained by catheterizing both ureters, evaluating the function of each kidney separately, then comparing the two. Only if there is a significant disparity of function between the two kidneys is the patient likely to benefit from surgical treatment, they report.

Angiotensin II has also been suspected of playing an important role in essential hypertension. Blood angiotensin levels have been reported to be higher in patients with benign essential hypertension than in normotensives, and were most strikingly elevated in patients with malignant hypertension. NHI grantees have reported radioactive tracer studies indicating that the metabolic inactivation of angiotensin proceeds more slowly in hypertensives than in normotensives, and may account for the higher angiotensin concentrations found in hypertension.

When properly applied, techniques developed and evaluated by NHI grantees make kidney biopsy a safe procedure that can be extremely valuable in the diagnosis of toxemia of pregnancy and also as a guide to its clinical management. In addition, the procedure may prove to be a valuable tool for gaining greater knowledge about the kidney in relation to pregnancy and its complications.

Surgery

Stokes-Adams syndrome results from damage produced by disease, infarcts, or atherosclerotic deposits in the heart's specialized conduction system, which originates and transmits the electrical impulses causing the heart muscle to contract. Victims of this disease may suffer unpredictable seizures that may produce uncoordinated contraction (fibrillation) or partial or complete heart block. NHI grantees report the successful long-term use of artificial cardiac pacemakers in patients with Stokes-Adams syndrome. The pacemaker is set at a pace suitable to maintain circulation adequate for normal activity. The power source is tiny enough to be implanted under the skin, thus eliminating external leads, and need be replaced only every 5 years or so.

The specialized conduction system may also be damaged inadvertently by heart surgeons while repairing ventricular septal defects. Especially vulnerable are the bundle of His and its branches, which run down the muscular wall (septum) separating the two ventricles. Since the paths followed by these elements may deviate considerably from normal in congenital heart disease, the heart surgeon needs a practical, reliable method for locating them accurately. Instrumentation and techniques devised by NHI grantees accurately locate the specialized conduction system by taking advantage of the fact that it offers less resistance to the flow of nerve impulses than does the heart muscle. The method has already demonstrated its simplicity and reliability in a number of heart operations.

Clots and lesions preventing an adequate supply of blood from reaching the brain are frequently located, not in the relatively inaccessible brain proper, but in segments of its supplying blood vessels lying in the neck or chest. Further, the obstructions are frequently confined to short segments of these blood vessels. NHI grantees report that removing or bypassing these lesions can frequently clear up the distressing symptoms of cerebral artery insufficiency in patients carefully selected on the basis of operable lesions.

Surgical removal of clots blocking large blood vessels is attended by the risk that the clot may re-form or that fresh clots might develop in collateral vessels, a risk not completely eliminated by anticoagulants. NHI grantees report that fibrinolytic therapy—the infusion of drugs which activate the body's own clot-dissolving mechanisms—is highly effective against such clots if treatment is begun promptly.

In heart operations requiring the use of the heart-lung machine, blood coagulability must be reduced, usually with heparin. After surgery, coagulability must be restored to reduce the threat of hemorrhage. This is usually done by using protamine or polybrene to neutralize the heparin. NHI grantees report that both are effective heparin neutralizers, but that excessive doses of either can themselves induce a clotting deficiency. Both can produce a deficiency of a clotting factor (factor VIII, or antihemophilic globulin) important to normal coagulability.

COMMUNITY PROGRAMS AND SERVICES

The purpose of the heart disease control program is to help minimize the effects of cardiovascular disease on the people of the United States. To do this the program provides professional, technical, and financial assistance to State and local health departments in applying knowledge presently available for preventing and controlling the heart diseases.

Large strides have been made in applied research and community services for heart patients. This is particularly apparent in such disease areas as strokes, rheumatic fever, and congenital heart disease. Many stroke programs, for example, have been started or expanded in recent months that reinforce earlier demonstrations that 80 percent or more of those who survive a cerebrovascular accident can be restored to self-care. These programs will receive continued emphasis in the coming year.

Prior to this year, the fluorescent antibody technique for the rapid identification of group A beta hemolytic streptococci (precursor to rheumatic fever) had been introduced, with program assistance, in all State and territorial health departments. Also, a technician in each State had been trained by the Public Health Service. In the current year, efforts have been focused upon meeting the need for training courses within States, to make the technique more readily available to physicians in many communities. Thirteen in-State courses, utilizing program equipment and personnel, have been held in 10 States, and approximately 200 public health and private laboratory technicians have been trained.

Similar courses have been tentatively scheduled in other communities that have requested them as far ahead as December 1962. A new exhibit, designed to acquaint pediatricians and general practitioners with the fluorescent antibody technique, was displayed at four national medical association meetings during the year. This program of professional education will be continued and expanded during the coming year.

Tape recordings and interpretations of 33,026 children's heart sounds were completed in Chicago, yielding 64 cases of definite organic heart disease, a rate of 2 cases per 1,000 children screened. Thirty-two of the cases had been previously unknown, and as a result of the project have received the benefit of medical care. The heart disease control program has since assembled less expensive and portable tape-recording equipment, from components recently made available on the commercial market. The new assembly is currently being tested in its first field trial in a North Dakota community.

As a result of interest aroused by the Chicago study, the heart disease control program has received 28 inquiries from 20 States concerning this screening method. Since there are still many questions to be answered before this technique can be recommended for nationwide use, the program has been encouraging additional studies to obtain the needed answers. Several areas have plans to do further research in this field.

Health departments, private physicians, and other medical and ancillary personnel have expressed a desire for the adaptation of electronic systems, utilizing computers as a central core, as an aid to the reading of electrocardiograms, and to relieve physicians of time-consuming work. This adaptation has been developed, and a continuing study and demonstration of the method is being made. In addition, plans are being developed for similar automation of the phonocardiogram, ballistocardiogram, and artiopulse. These and other newer methods may be of importance in improving the diagnosis of heart disease, an area of real need and great significance for the phyiscian and his patients.

Over 50 percent of all public health nursing services in the country relate in some way to the care of patients with heart disease. It has been recognized that the improvement of services to heart patients can be accomplished more effectively by providing better training and educational material to nurses. To meet this need, the program has fostered and supported the development of a magazine on cardiovascular-renal diseases which will ultimately be published and distributed to over half a million of the country's nurses.

The appropriation increase in fiscal year 1962 made it possible for the program to assign a total of 111 medical officers and other professional persons to assist States in improving and expanding their heart disease control activities. This represented more than a 50 percent increase over the previous year in the number of professional persons assigned from this program to work actively in conducting stroke rehabilitation programs, rheumatic fever prophylaxis programs, field studies of coronary disease, and general demonstrations and tests to improve diagnosis and patient care. Several medical officers are receiving advanced training in schools of public health and other professional schools. This specialized training will enable them to provide better assistance and services to health departments across the country in future years.

SUMMARY OF APPROPRIATIONS REQUEST

The appropriation request for 1963 is $126,898,000. This amount will provide for program expansion in the following areas:

Research projects.—Additional grants in support of new research in arteriosclerosis, cerebrovascular disease, hypertension, congenital heart disease, rheumatic fever and rheumatic heart disease, heart failure, coagulation defects, cardiopulmonary diseases, and other diseases of the blood and blood vessels.

Direct research.—Conversion of space from organic chemistry use to biochemistry laboratories; creation of a pure helium atmospheric environment for studies of oxygen-sensitive enzyme systems; development of realistic mathematical models of the cardiovascular system; expansion of metabolic studies of catechol amines and lipids.

Collaborative studies.—Expansion of epidemiological studies to include familial factors; development and initiation of studies in the pathology of cardiovascular disorders, both domestic and foreign.

Professional and technical assistance.—Increased consultative services in connection with State control programs in hypertension, congestive heart failure, and strokes.

Review and approval of grants.—Support of increased activities of the Institute staff and National Advisory Heart Council necessary to the grants program.

The request for 1963 is distributed among program activities as follows:

Grants and related contracts:	
Research	$89, 720, 000
Fellowships	3, 615, 000
Training	10, 539, 000
State control programs	5, 000, 000
Subtotal, grants	108, 874, 000
Direct operations:	
Research	9, 985, 000
Collaborative studies	1, 330, 000
Training activities	186, 000
Professional and technical assistance	4, 111, 000
Review and approval of grants	1, 958, 000
Administration	454, 000
Gerontology Building	380, 000
Subtotal, direct operations	18, 404, 000
Total 1963 obligations	127, 278, 000
Less balance transferred from prior years	—380, 000
Total 1963 appropriation request	126, 898, 000

SUMMARY OF DEVELOPMENTS DURING LAST YEAR

Dr. Knutti. Mr. Chairman and members of the committee, this was a productive year for the National Heart Institute, with strengthened activities in the Institute's total program. Basic and clinical research studies showed steady growth and encouraging results. Research efforts advanced not only in Bethesda but also in hundreds of U.S. institutions receiving heart grant support. Community heart programs also expanded their services and developed new ones.

A special report on highlights of heart progress has been developed and we are prepared to submit that for the record.

In addition, new developments in program areas—closely linked with substantive research—advanced the goals of the National Heart Institute. Nine new grants for heart program projects (centers) were awarded, bringing the total to 26.

And I might add that 20 more such requests will be reviewed by the National Advisory Heart Council next month.

Grants were awarded for two additional primate research centers, and a third application is pending. Heart Institute participation in international research has increased and embraces such things as research projects, collaborative studies, and some intramural interests.

The Heart Institute strengthened its organization in biometrics and epidemiology. Negotiations for a new gerontological research facility in Baltimore were begun, in accordance with the appropriation of funds for planning purposes. Seeking improvement of scientific communications, the Institute continued its cooperation with the National Library of Medicine and other concerned agencies.

The Heart Institute's program of intramural research made substantial gains during the year. The complex processes of fat metabolism, the mechanisms that regulate blood pressure and modify heart output, and the surgical management of congenital heart defects exemplify areas that yielded significant gains.

Many promising developments, covering a wide range of medical progress, were also reported from grant-supported institutions and investigators. Research training, another important program, is currently supporting approximately 320 undergraduate and graduate training programs.

Although the year can be characterized as a productive one, it was simultaneously a year for an increasing toll of heart disease deaths. Over 900,000 citizens died from heart disease last year, well over half of all deaths in the United States, with at least 1 person dying from heart disease every minute.

In conclusion, Mr. Chairman, the request for the National Heart Institute is $127,278,000 as compared with $112,389,000 available in 1962. The request for 1963 will provide for an increase of $13,684,000 in research grants; an increase of $203,000 in direct research programs of the Institute; an increase of $439,000 in collaborative studies (biometry, epidemiology, and geographic disease aspects); an increase of $111,000 for professional and technical assistance to States; an increase of $124,000 in review and approval activities of professional and clerical staff and heart council; and an increase of $568,000 representing this Institute's share of costs for research and clinical supporting services, and for review and approval and administrative services furnished centrally. This is partially offset by a reduction of $240,000 in costs of developing plans and specifications for a heart-gerontology building.

That concludes, Mr. Chairman, the summary of my prepared statement.

RESEARCH ACCOMPLISHMENTS

With your permission, I would like to speak for a moment about some research accomplishments and some specific problems that have come into our institute.

Mr. Fogarty. Do you think the heart institute can be as proud as the mental-health institute was this morning about the accomplishments in the past year?

Dr. Knutti. In our sphere of interests, I think we have as much to be proud of.

Mr. Fogarty. Heart disease still kills more people than all others put together, does it not?

Dr. Knutti. Yes, sir.

Mr. Fogarty. If we decide to increase your appropriation and we get up on the floor of Congress and some Member who does not believe in research says, "You are asking us to appropriate $127 million and you have been giving us the same story for 10 or 12 years, now. You still tell us that it causes more deaths than all other diseases put together"; what is my answer to a charge like that? What is the best answer I can give as a layman when someone questions the continued high expenditures in this field of research and claims the expenditures so far haven't accomplished much?

Dr. Knutti. We have learned much about heart disease in the past 15 to 20 years. We are learning at a greater rate than we have learned in the past. We have more people studying the various facets of this very complex situation than ever before. We still have many more problems to be solved. We really have but scratched the surface as far as our fundamental and basic knowledge is concerned.

Mr. FOGARTY. Doctor that would not be a good answer to me. If I were in your position, I would be thinking of some specific examples of real advances in the last 4 or 5 years because of the Federal Government spending money—new areas of surgery that have been opened up in the last few years, some of the drugs that have been developed in the last few years, and other things like that.

Dr. KNUTTI. I can submit a detailed statement on that.

Mr. FOGARTY. Well, let us do it now and we will give you the opportunity of expanding on it in the record, if you think it will make it any stronger.

Dr. KNUTTI. One item that has been found recently through epidemiologic studies has been the relationship of diet to heart disease, particularly to coronary disease. These clues have been arrived at from epidemologic studies; that is, from studies of populations, very carefully selected population groups, some of which differ very sharply in their mortality from coronary heart disease and atherosclerosis.

Such studies have accumulated enough evidence against cholesterol and saturated fats to make these two substances prime suspects in their relationship to atherosclerosis.

Mr. FOGARTY. That is about all they are, is suspects; are they not?

Dr. KNUTTI. Yes, sir.

Mr. FOGARTY. We have doctors that have been quoted as saying they do not know whether the amount of cholesterol intake has any bearing on heart disease or not.

Dr. KNUTTI. I think we really do not know positively, but there is enough evidence, enough straws in the wind, to make it urgently necessary to find out just exactly what this relationship is.

Mr. FOGARTY. Most doctors now would prescribe a low-fat diet if you are a potential victim or if you have had a coronary?

Dr. KNUTTI. I suppose this would depend upon the individual opinions of the physician as well as the condition of the patient. It is a controversial subject. And I should suspect that the conservative individual who believed that this was, in effect, the case, would do that.

CHOLESTEROL-LOWERING DRUGS

Mr. FOGARTY. Are there any drugs that will lower your cholesterol level?

Dr. KNUTTI. Yes, sir.

Mr. FOGARTY. Which ones?

Dr. KNUTTI. One that has received quite a bit of publicity and study, as well, is MER–29. This is a drug which is effective in lowering blood cholesterol.

Since the time this effect was discussed there has been a considerable amount of work done with this particular compound and we know more about its mechanism in lowering cholesterol levels.

There are other substances——

Mr. FOGARTY. Doesn't MER–29 have side effects that are undesirable?

Dr. KNUTTI. Very recently there have been reported some side effects. From the best information we have been able to obtain, this has occurred in only a few of a large number of patients who received the drug.

Mr. Fogarty. It seems to me I remember the manufacturers themselves have become a little concerned about it, and notified the professional groups and individual doctors about some of these possible side effects.

Dr. Knutti. That is correct, sir. The manufacturers sent a flyer to physicians in regard to this.

SPECIFIC EXAMPLES OF RESULTS OF HEART RESEARCH

Mr. Fogarty. Dr. Knutti, I believe I interrupted you. Give me four or five good examples of what has been accomplished due to increased spending for research.

Get up a statement and put it in the record at this point.

Dr. Knutti. All right, sir.

(The requested information follows:)

Accomplishments Against Heart Disease

The accomplishments of recent years against heart disease, illustrated with examples of research progress, reveal two paramount facts. First is the fact that more cardiovascular knowledge has been accrued in these years than in all the past. Considerable gains have been made both in basic knowledge and in findings to benefit actual or potential victims of heart disease. Second is the fact that these advances, considered in relation to the nature and toll of the problem of heart disease, provide basis for furtherance of the nationwide attack on this No. 1 cause of death.

There should not be cause for despair over the large number of heart disease deaths, just as there should not be cause for complacency over the achievements to date. The total number of heart deaths is increased each year because our population is increasing. There also are increasing numbers of people living into older and older age brackets, where heart disease is even more prevalent over other causes of death than in younger years. Many of these older victims of heart disease would have died earlier had there not been progress making possible extension of life. Thus, the rate at which heart disease strikes, the number of deaths per 100,000 population, has been slowed down and is slightly declining. Moreover, major research breakthroughs could bring about a slowing down or stopping of the increase in total numbers of heart disease deaths. The record of past progress and growing cardiovascular knowledge make such a conquest of heart disease through an all-out attack a strong probability rather than a speculative possibility.

Research has made such progress that most kinds of congenital heart disease, once considered incurable, can now be cured or ameliorated. Some of these defects are being prevented by improvements in prenatal care. Most kinds that do occur can now be precisely diagnosed and then helped by surgery. A few years ago surgeons could benefit only five types of congenital heart disease; and it was thought that there were only a dozen or so kinds. Today, some 35 kinds are recognizable, but surgery can correct many of these and almost all of the major kinds. Research developments in heart physiology, heart-lung machines, hypothermia for open-heart operations, and important advances in diagnostic methods have helped make this possible.

Rheumatic fever and rheumatic heart disease are also a field of progress. Initial attacks of rheumatic fever can be prevented by prompt, adequate antibiotic treatment of the streptococcal infection which almost always precedes a first attack. Research has recently developed a rapid, accurate test for the physician to identify and locate streptococci. Then, by treatment, first attacks can be prevented. Even when rheumatic fever does occur, damage to the heart can be avoided by preventing further attacks through antibiotic or sulfonamide prophylaxis. Even if the heart is damaged, in many cases surgical repair is now possible. Thus, this kind of heart disease is being reduced substantially.

Through research, also, many valuable drugs have been developed against hypertension. Only a few years ago there were almost no effective desirable agents for reducing it. Therapeutic agents, constantly improving through continuing research, can today lessen the severity of hypertension in most patients and control it adequately in many others. Recently, also, surgical repair of the arteries of the kidneys has been found helpful for certain hypertensive patients.

Arteriosclerosis and atherosclerosis—diseases of the arteries which lead to most heart attacks and strokes—were until recently considered degenerative disease, an inevitable, irreversible part of the aging process and among the most hopeless of diseases with respect to treatment. Research has shown that this is not so and is uncovering more and more knowledge of the causes, now known to be complex and multifaceted. Meanwhile, recent progress has brought treatment and management of patients considerable improvements. Drugs, surgery, and diet, separately or in combination, are used to benefit victims of arteriosclerosis. Anticlotting agents can greatly reduce the incidence of heart attacks, severity of heart muscle damage from coronary occlusion, and incidence of recurrence. Dietary measures under the physician's guidance are another aid in the disease's management. Surgery can also benefit many, as, for example, in recently developed operations to remove or bypass many lesions or blood clots affecting the larger blood vessels.

This broad picture of accomplishments against the major kinds of heart disease—a complex of over 20 diseases of the heart and circulatory system—is further illuminated by citing a few interesting examples of the many hundreds of specific research accomplishments reported in the past year alone:

> Improvement in knowledge enabling the physician to spot "high risk" individuals before a stroke or heart attack occurs (based on evidence from the National Heart Institute Framingham heart study and other epidemiological studies).
>
> Information on the nature and operation of the hitherto little-studied cholesterol precursor, desmosterol, which may be important in atherosclerosis.
>
> Artery reconstruction operations to benefit many stroke patients, as shown by a study of 895 patients reported on in 1961.
>
> A new technique, "counterpulsation," to increase collateral circulation in the blood-starved hearts of coronary attack victims through a new pump helping to open standby systems of heart arteries.
>
> Electronics research developments such as a system for continuous electrocardiography study of a person over long periods, by means of portable, miniature electrocardiorecorders carried by patients in their pockets and by electronic machine analysis rapidly of the resulting voluminous data.
>
> Studies of experimental compounds for hypertension, such as National Heart Institute studies of two drugs, different in their mode of action, which from fundamental and early clinical experimentation appear promising as to effectiveness and toxicity characteristics.

In sum, with regard both to accomplishments to date and prospective for the future, it is a great mobilization of resources and the informed interest and support of the Congress that make possible the record of progress and accomplishment. Some kinds of cardiovascular disease can now be prevented, others cured. Some kinds, including some once considered incurable or inevitably fatal, can be ameliorated or reversed. Most patients with any kind of heart disease can be materially benefitted by proper treatment.

Despite these achievements, the remaining bulk of the problem of heart disease is vast, and much more remains to be done than has been accomplished. There is scientific confidence, however, that through their continuance and strengthening, the Nation's heart resources will uncover and put to use the needed information on causes, cures, and preventives that will mean major breakthroughs against the leading cause of death in the United States.

THE 1963 BUDGET REQUEST

Mr. Fogarty. The appropriation for 1962 is $132,912,000, and the request for 1963 is $126,898,000. This is a reduction of $6,014,000. Is that right?

Dr. Knutti. I believe that is correct.

Mr. Seggel. Yes; that is right.

EFFECT OF 1962 RESERVE

Mr. Fogarty. So this is another program that is not even going to get back the 1962 reserve; is that correct?

Mr. Seggel. That is right. The 1963 request will not get to the total appropriation for 1962.

Mr. Fogarty. So much of the 1962 reserve is going to be lost and never recovered in an area that causes more deaths than all the other diseases known to medicine; is that right?

Mr. Seggel. Yes, sir.

Mr. Kelly. There are in this item some nonrecurring costs in 1962 that I think should be noted, Mr. Chairman.

Mr. Fogarty. I know, but still we are not going to get back the amount that was put in reserve in 1962.

Your reserve is $19,595,000. This is the greatest killer of all, and it is the highest reserve applied to any one of the institutes.

How much of this is for forced savings?

Mr. Kelly. $13,370,000.

Mr. Fogarty. $13,370,000. This is going to be a real jolt for you in 1963, too, Doctor.

The reserve for forced savings is the largest in the Department; in fact, just this one appropriation is bearing over 20 percent of entire forced savings of the Department; is that right?

Mr. Kelly. Yes, sir.

Mr. Fogarty. Twenty percent.

This is the worst example I have seen of this cut in the budget for 1962. I just cannot understand it. These cuts seem to get worse as we go along. It seems to me that if the President knew the details of this, he would never have gone along with the Department's suggestion.

Now, what does the other part of your reserve represent, Doctor?

Dr. Knutti. The difference between the 13 and the 19?

Mr. Fogarty. Yes.

Dr. Knutti. Well, this was a self-imposed reserve.

Mr. Fogarty. For what reason?

Dr. Shannon. Mr. Fogarty, that was primarily a reserve imposed against the center program, because it was felt that this program could not develop as rapidly as had been projected in the appropriation. Of the $6,225,000 voluntary reserve $6 million was taken in the research grant area.

UNFINANCED TRAINING GRANTS

Mr. Fogarty. Do you have any requests for good training programs that you cannot finance?

Dr. Knutti. Yes, sir.

Mr. Fogarty. Give me a couple of examples, and then you can expand on that in the record, because I want a complete answer on this.

Dr. Knutti. I do not have the exact figures, sir, but I can supply them.

Mr. Fogarty. All right.

Dr. Knutti. We have nearly a million dollars of unfinanced training grants.

(The requested information follows:)

The unpaid grants range over a variety of scientific fields, all of which focus upon training for research in the cardiovascular area. One might select some examples from these unpaid grants and make the following comments:

(1) Investigations of the causes, diagnosis, and prevention or treatment of heart disease have always been of great interest to the National Advisory Heart Council and its advisory study sections. Attention has been repeatedly called to the dearth of good research training opportunities in pediatric cardiology. The activation of the two approved grants in this field would provide support to an additional five trainees each year.

(2) From the viewpoint of the National Heart Institute Training Committee and the National Advisory Heart Council, training grants which aim to strengthen the interdisciplinary competence of persons training for careers as research scientists are highly desirable. These grants represent programs where two or more laboratories or departments with related research interest pool their training resources, and several of these multidepartmental grants, which would support about seven trainees per year, are pending payment.

(3) Among the unpaid grants are six involving awards to be made to outstanding hospitals which are unaffiliated with medical schools. The National Advisory Heart Council and the Training Committee have been interested in studying the potential of these institutions as a source for providing research training outside the medical school setting. This experimental program can hardly be put to the test unless a sufficient number of hospitals participate.

Mr. Seggel. The projected deficit is $1,142,000 in fellowships and $928,000 in training grants.

Mr. Fogarty. So between fellowships and training grants, about $2 million.

Dr. Shannon. That is right.

Mr. Fogarty. What year are you talking about?

Mr. Seggel. That is this year.

Dr. Shannon. 1962.

TRAINING GRANTS FOR 1963

Mr. Fogarty. All right, tell us about 1963.

Dr. Shannon. Research grants or training grants, Mr. Fogarty?

Mr. Fogarty. Training grants. I am talking about training grants and fellowships right now.

Dr. Shannon. I think it will be difficult to give specific figures for training because they have just received the manpower report and have it under study.

Mr. Fogarty. All right, we will let that go until you report in 2 weeks on this overall report on manpower.

RESEARCH GRANTS BACKLOG PROJECTED FOR 1963

Under this budget, you are going to have a backlog of 446 research projects in 1963, totaling $7,827,000.

Dr. Shannon. Yes, sir.

Dr. Knutti. That is correct.

Mr. Fogarty. That is not progress, is it, Doctor, when you are going to have that backlog in approved research projects?

Dr Knutti. It will not be possible to award all approved research projects.

Mr. Fogarty. Well, on the basis of these figures, I maintain that you are going backward.

CLINICAL DRUG TRIALS

Mr. Fogarty. Last year in our report we said that we would expect you to expand your activities with regard to clinical drug trials. What are you doing in that activity?

Dr. Knutti. We have planned a rather extensive collaborative study in which various drugs and substances which are known to lower cholesterol are concerned. This was started out as the result of a study by a committee headed by Dr. Robert Wilkins, a member of the National Advisory Heart Council, who is professor of medicine at Boston University.

Feasibility studies have been completed, and it has been recommended that this type of study is indeed practical. The study is in the stage of planning at this point, whereby a common protocol which can be followed quite accurately by all participants in the study is being worked out. This is in order to make sure that the results obtained by the 20 to 30 investigators who will collaborate will get completely comparable results.

This type of thing will take some time. We are proceeding as rapidly as possible; however, the program probably will not get launched until fiscal 1963.

It will be a relatively long-term project, and it will ultimately be quite expensive. The estimate for the first year, while things are getting tooled up, may not exceed more than half a million dollars. But, as new investigators are added and as the program really gets underway, it might cost up to $1 or $2 million a year.

BUDGET FOR 1963

Mr. Fogarty. What do you have in the budget for 1963 for this purpose?

Dr. Knutti. This would be included under the research grants item, sir.

Mr. Fogarty. What do you think you will use?

Dr. Knutti. A total of $72,895,000 for research grants.

This does not include the projection of $7,827,000 that was estimated for 1963 referred to earlier.

Dr. Shannon. Mr. Fogarty, they have a total projection for 1963 of approved projects of $80,722,000, for which the 1963 budget provides $72,895,000. The program that has just been described is contained within those projections.

Mr. Fogarty. In the $72 million?

Dr. Shannon. Yes.

I believe that it will be possible to get the program off the ground within the $72,895,000.

Mr. Fogarty. Well, we are going to expect it.

ANTICOAGULANT DRUGS

What about anticoagulant drugs? Have they improved in the last 3 or 4 or 5 years?

Dr. Shannon. There has been no substantial improvement in drugs, Mr. Fogarty; there has been an improvement in usage. Would you say that?

Dr. Knutti. That is correct.

Mr. FOGARTY. Are you doing any work in the area of hemophilia? That would be just the opposite, would it not, in trying to develop drugs that would coagulate the blood?

Dr. SHANNON. There are a limited number of projects, but I think most of them would be found in the Arthritis Institute rather than the Heart Institute.

RESEARCH WORK ON STROKES

Mr. FOGARTY. What about strokes? Are you doing more work in the Heart Institute in strokes, or are people in the Institute on Neurology doing more?

Dr. KNUTTI. We are collaborating with the Neurology Institute. A joint committee has been formed, in which both the Neurology Institute and the Heart Institute have an interest.

Mr. FOGARTY. Some neurologists claim that they know more about strokes than the heart specialist does.

Dr. SHANNON. Mr. Fogarty, this is an example of a field that can be approached either from the point of view of the neurologist or of the point of view of the cardiovascular physiologist or cardiologist.

But in point of fact, the definitive exploration of the field requires the collaboration of these two groups.

It is interesting that at NIH there developed, during the last 3 or 4 years, a rather intensive rivalry between two councils who have responsibility for these respective areas, and each council attempted to get programs off under its own steam. During the past year to 18 months, it has been possible to bring them together, and we feel we now have, under this joint sponsorship, quite a systematic and effective program.

This involves not only problems resulting from cerebrovascular accident but extends even to such things as corrective surgery and the like. The scope of these studies is very broad.

BALTIMORE GERONTOLOGY FACILITY

Mr. FOGARTY. Last year's appropriation included $1 million for plans and specifications for a gerontological facility in Baltimore. This request was justified in the Senate. So we would like you to give us a few details on what this will be, how your plans are progressing, and what you estimate the total costs will be, what activities will be carried out there, and how they will be financed.

Dr. KNUTTI. This arose as a result of the fact that Dr. Nathan Shock, who is a member of the staff of the National Heart Institute, has for many years carried on outstanding gerontological research at the Baltimore City Hospital. He has been allowed to use patients who come into that hospital for his studies in this area, and the Baltimore City Hospital has liberally supplied him with space.

I would amend that to say that the Baltimore City Hospital started out giving him adequate space, but as the program has grown; the need for more research has grown, so that ultimately he was really breaking at the seams for additional space which has not been available.

In the meantime there has developed in the——

Mr. FOGARTY. Are you doing some work in the U.S. Public Health Service hospital over there, too?

Mr. Kelly. Yes, sir.

Dr. Terry. During the period, Mr. Fogarty, after the National Heart Institute was created and prior to the time we had clinical facilities at the NIH, we operated a very active clinical research program. As a matter of fact, I was in charge of that program, and we built up a staff and experimental program which eventually moved to the National Institutes of Health.

When we moved over, it left essentially nothing of that unit in the Baltimore hospital.

Since that time, we have been attempting, with the staff in the Division of Hospitals, to build up some appropriate clinical research activities in our hospital, and we have some activities going there today. But it is nothing like the intensity of the type of program we had there from 1950 to 1953.

Mr. Fogarty. All right, go ahead, Doctor.

Dr. Knutti. At any rate, Dr. Shock was severely lacking in space. In the meantime, his research had attracted the interest of a number of the staff of the Baltimore City Hospital. And as I understand the story, there were a number of very competent individuals who were on the staff of the Baltimore City as well as Johns Hopkins or the University of Maryland, who developed interests in gerontological research.

This was the background that led to the need for consideration of more space for the total gerontology effort, at the Baltimore City Hospital.

On the basis of justification of this need, the Congress last year allowed $1 million for planning, and I would be glad to tell you what has happened since that time.

ARCHITECTURAL REQUIREMENTS

Mr. Fogarty. All right, tell us how much it is going to cost and when it is going to be completed, and what you expect to carry out in this building.

Dr. Knutti. I might say, sir, that it has been somewhat more complicated than anticipated. This business of putting up, on land that will be deeded to the Government by the City of Baltimore, a Federal structure that will include individuals who are not Government employees has taken time to work out in detail. We feel at the present time that this has been accomplished. We have a general plan of operation and know approximately how much space will be occupied in the building and by whom.

We are now ready to submit the plans to architects. This has been gone over by the engineers of the Public Health Service and the NIH, and we hope, as a matter of fact, within the next week, to carry it to the stage where definitive plans relative to the exact nature of the building will be drawn up.

DESCRIPTION OF FACILITIES

Briefly, however, the present planning visualizes about 90,000 square feet. Roughly 40,000 square feet of this space will be occupied by Dr. Shock and his collaborators. There will be certain laboratories available for visiting scientists who wish to work on either Dr. Shock's colony of old rats, which is, incidentally, a goldmine for this type of research, or on problems of their own related to gerontology.

In addition, there will be space provided for the research workers on the staff of the Baltimore City Hospital, and the staff of Johns Hopkins University or Maryland University who are also on the staff of the Baltimore City Hospital.

Of course, there will be laboratory facilities and all of the ancillary services that are necessary for the operation of a research building.

One of the expenses connected with the building is going to be the cost of improving the heating plant at the Baltimore City Hospital and the electrical conduits to make it possible for them to furnish heat and power to the building. Our engineers have estimated that this alone will cost about $1,500,000.

TOTAL COST

The estimated cost of the 90,000-square-foot building, I have been told, will be in the neighborhood of $8 million. So this would make a total outlay, including the planning, of approximately $10 million; perhaps more.

Mr. **Fogarty**. You do not expect to start construction in 1963, then, do you?

Dr. **Knutti**. In fiscal year 1963; no, sir.

Dr. **Shannon**. Mr. Chairman, for the purposes of the record, could I give——

BACKGROUND OF PROPOSAL

Mr. **Fogarty**. Who justified this before the Senate last year?

Dr. **Shannon**. Dr. Watt. I think it might be helpful for this record to give some of the broader background. It happened before Dr. Knutti's time.

Mr. **Fogarty**. I know.

Dr. **Shannon**. As you know, Mr. Chairman, there was established within the NIH—later within the framework of the Baltimore City Hospital—a laboratory on gerontology. This was in the period 1940–42. This constituted the first attempt on the part of the Public Health Service to study what happens to a human individual as he ages.

This developed during the 1940's. Until the latter part of 1949 it was the only comprehensive gerontological laboratory in the country. At the time the Heart Institute was established, this was transferred to the Heart Institute to provide a solid home for its future development.

Very early in the course of the Heart Institute's custodianship of the laboratory, the facilities were expanded to about twice the size they had been previously as the result of an appreciation by the Welfare Department of Baltimore City and the Baltimore City Hospital, which is part of the Department of Welfare, of the importance of this type of research to a stable community such as Baltimore.

At the time full-time services were provided for the Baltimore City Hospital, primarily from the Hopkins Hospital, in the form of chiefs of medicine, chiefs of surgery, and chiefs of neurology. When the expanded facilities became available, beginning in about 1952 or 1953, Dr. Shock was able to elicit the interest of these chiefs of service in the programs that related to a definition of what constitutes aging. At that time he was concerned with organ aging, trying to determine whether or not aging was characterized by loss of substance, or by changes in the ability of an organ to respond.

DEFINITION OF AGING

Mr. Fogarty. What is your definition of aging?

Dr. Shannon. Well, in terms of Dr. Shock's biological studies, aging is the process which is the net effect of loss of organ substance with time.

In other words, the kidney cells of the aged are precisely the same as the kidney cells of the young, but there are fewer of them. The liver cells of the aged are precisely the same as the liver cells of the young, but there are fewer of them. The insults of infection and disease in time reduce the amount of organ tissue and decrease the capacity of the individual to resist.

This was a rather startling generalization that obtained for the organs of the body, for the central nervous system, and for certain organs of reflex activity. From Dr. Shock's results, it was quite apparent that, biologically, the individual who had aged had many capabilities he had heretofore not been thought to have, but he had them in lesser amounts, rather than qualitatively of a different sort.

CENTERS FOR RESEARCH ON AGING

Now, the thing that precipitated this building and this development in Baltimore was the Commission on Aging, the genesis of which, Mr. Fogarty, you are well aware.

This happened about 2 years after we had begun a program to establish aging centers within university structures, but had not had much success. We had one at Duke and another at Brown but these had not developed comprehensive research approaches that involved studies that went from the biological right on to the sociosomatic aspects of aging. They had rather limited studies and, although they did group many disciplines together to take a look at the total problem, they did not evolve into a comprehensive program.

When the Commission on Aging proposed a real forward stride in the development of studies on aging, since we had not been able to establish broad studies within the university structure, we looked at the Baltimore operation and realized that we had in Baltimore the elements of precisely the type of broad institute that we were seeking. It was on the basis of this appreciation, the willingness of the Department of Welfare of Baltimore City, and the willingness of the hospital system of Baltimore City, and the willingness—or the anxiety—of Hopkins and the University of Maryland to get on with the job that this type of joint enterprise was undertaken.

Our agreement is that we will furnish the structure. We will furnish support for the research that is contained within approximately half of the structure out of our direct operation. This would be a continuation of Dr. Shock's activity. The remaining work can be supported either by the university or by grants that they might obtain through us.

So what we have now, as the result of these negotiations, is the beginning of an actual broad center on aging. It will, incidentally, also house the Maryland Commission on Aging, so that some of the studies that begin in the hospital can, in fact, extend into the community, whether this community be Baltimore or the rural areas.

We are very excited about this project because for the first time there will be created a multifacet institute that can study the problems of aging both in the hospital and in experimental animals and in the community.

It has the further advantage of having the full support of the social services of the welfare department of the city and is integrated in a very active State program.

So we think this is a very well-worth-while activity.

Mr. Fogarty. Now, the program at Duke is 3 or 4 years old. The one you mentioned at Brown is just getting started. They just received their grant, so they have not had a chance to develop much yet.

Dr. Shannon. No; this will be a small program oriented, primarily, to the biology of the aging process.

Statements on Various Phases of Heart Research

Mr. Fogarty. All right, Doctor, you have several special statements on various phases of your research. We will place them in the record at this point.

(The requested information follows:)

Atherosclerosis and Coronary Heart Disease

Although diet and hormones have been the most intensively studied factors affecting the development of atherosclerosis, environmental and emotional factors are currently receiving increased attention.

Emotional stress has been shown to produce striking elevations in serum cholesterol levels. More recent studies by NHI grantees indicate that stress also exerts profound effects on serum lipoprotein patterns. During the stressful period of final examinations, medical students exhibited a sharp increase in serum levels of low-density lipoproteins, but little or no change in their high-density lipoprotein fraction. A preponderance of low-density lipoproteins, which transport most of the cholesterol and neutral fat of serum, is associated with relative proneness to atherosclerosis. This fraction also appears to be extremely sensitive to emotional stimuli.

Other grantee studies evaluated the effects of disturbed living conditions on the atherogenic response of cockerels, who form a social order much like man's. Disturbing this social order by isolating these cockerels from other birds enhanced the development of atherosclerosis in cockerels fed an atherogenic diet. It also retarded the regression of established atherosclerotic lesions in these birds.

Other grantee studies, evaluating the response to cigarette smoking in normal subjects and in subjects with established heart disease (myocardial infarction), revealed that cigarette smoking produced a striking increase in serum levels of free fatty acids. Within 10 to 20 minutes after the subjects had smoked two cigarettes, free fatty acid levels increased by about 30 percent in the normal subjects and by about 65.5 percent in the patients with heart disease. The increase appeared to result from the nicotine-induced release of norepinephrine and epinephrine, both potent fat-mobilizing hormones. The sharper rise observed in the patients with heart disease may have been due to a greater release of norepinephrine and epinephrine or to decreased utilization of the fatty acids released by these amines.

Nicotinic acid appears to be a highly effective drug for reducing elevated serum cholesterol levels. It produces few undesirable side effects—chiefly flushing and gastrointestinal disturbances—and these are seldom severe enough to make it necessary to discontinue therapy. The drug is even more effective in reducing serum cholesterol when used in combination with diets low in total fat and saturated fat and containing larger proportions of highly unsaturated fats.

The tissue damage incurred by the heart during an attack causes it to release enzymes from the injured tissues. Elevated serum levels of such enzymes as GOT or lactic dehydrogenase are frequently helpful in diagnosing heart attacks even if the patient has put off seeing a doctor for several days. However, serum levels of GOT may also be elevated in the absence of a heart attack if the patient is suffering from cirrhosis, hepatitis, and other disorders. NHI grantees report that serum manganese determinations provide a valuable confirmatory test for myocardia infraction when the serum enzyme picture is clouded by other disorders. They report that after a heart attack, the heart releases about 60 percent of its manganese. Serum manganese levels begin to rise about 8–10 hours after the attack and remain elevated for 5–6 days.

Recent advances in instrumentation now make it possible to obtain electrocardiograms from actively exercising subjects without interfering with that activity and to monitor the electrical activity of the heart continously under normal life conditions. EKG data obtained during attacks of angina and subsequent treatment with nitroglycerine, and during eating, exercise, periods of excitement, and emotional stress have provided information on heart function not previously available. Data obtained from patients with suspected heart disease during physical activity have frequently confirmed questionable diagnoses.

THE CORONARY PROFILE

The diagnosis of atherosclerosis and coronary heart disease during their early stages is one of the major problems facing clinical investigators. At present, early diagnosis is almost impossible, because the diseases seldom produce any overt symptoms until they are well advanced. Even severe cases may produce no clinical manifestations until deposits or clots have so reduced blood flow to the affected part as to cause pain or tissue damage.

Yet, the greatest hope for materially reducing the heavy toll presently being levied by these diseases lies in prevention. The problem is to spot the coronary-prone individual early enough to institute preventive measures before these diseases have gained too much ground.

Data from many studies on human population have enabled scientists to construct a highly useful portrait of the coronary-prone individual. In general, he tends to have high blood pressure and elevated serum lipids, to be overweight, to smoke too much and exercise too little. He may be a hard-driving, aggressive (but sedentary) type who reacts strongly to emotional stress. He frequently has a strong family history of heart disease.

High blood pressure and high serum lipid levels, especially in combination, are probably the characteristics most dangerous to the coronary-prone individual; however, all of them are associated with increased risk of developing heart disease. The more of the characteristics the individual has, the greater his risk.

Of course, the coronary-prone individual can do very little about his ancestors. However, with commonsense and the aid of his doctor, he can do something about all of the other predisposing factors and thereby substantially reduce his risk of developing heart disease.

Recent findings from a long-term study among male employees of a Chicago utility company revealed that a large number of the subjects had signs of heart disease that were sufficient to arouse suspicion, but not adequate to establish a definite diagnosis. The category of suspect coronary heart disease was used to designate those subjects in which angina, myocardial infarction, or coronary insufficiency were suspected but could not be clinically confirmed. It was also used to designate subjects with EKG abnormalities that could not be definitely ascribed to coronary disease.

The study revealed a higher incidence of suspect coronary heart disease (122 cases per 1,000), than of overt heart disease (43 cases per 1,000) among the employees. The incidence of suspect coronary heart disease was higher among subjects who were overweight, who had elevated serum cholesterol, or who had hypertension; and was highest in subjects with more than one of these abnormalities. The study indicated that prompt measures should be instituted to correct risk-increasing abnormalities in subjects with suspect coronary heart disease, since their risk of developing overt heart disease appeared to be two to three times as great as that of subjects without symptoms.

HYPERTENSION

The cause or causes of hypertension remain obscure. Fortunately, however, this fact has not prevented the development of a number of drugs that are highly effective in reducing blood pressure in hypertensive patients. Further, many of the newer ones are highly specific in their actions and thus produce relatively few undesirable side effects.

Most of the drugs currently used against hypertension interfere with the transmission of nerve impulses between sympathetic nerve terminals and the muscles of the blood vessel wall. As a result, sympathetic nerve messages calling for arteriolar constriction cannot get through to their target organs. These drugs usually impede nerve traffic by interfering in one way or another with the action of norepinephrine, the chemical transmitter at most sympathetic terminals.

Alpha-methyl DOPA, a guanethidine, reserpine, and a number of reserpine analogs block the ability of the nerve terminal area to store norepinephrine. This action eventually depletes the terminal of so much of its norepinephrine that nerve impulse transmission is severely impaired. Recent NHI studies indicate that the free norepinephrine kept on tap for handling nerve traffic is prevented from diffusing out of its cellular storage sites by an active transport mechanism. Reserpine and other drugs that block norepinephrine storage appear to do so by knocking out this mechanism.

The norepinephrine is thus freed to leave the relative safety of the storage site. Some of it reacts with its receptors, much of it is promptly set upon and destroyed by enzymes, and the rest diffuses passively away from the terminal area to be eventually taken up by other tissues or destroyed.

Another group of drugs that lower blood pressure are the monoamine oxidase inhibitors. One of these, MO–911 (Abbott), appears to combine high potency as a hypotensive agent with low toxicity. These drugs inhibit monoamine oxidase, the enzyme chiefly responsible for destroying norepinephrine in most tissues. It is not yet clear why inhibiting this enzyme causes blood pressure to go down, but there is strong evidence that enzyme inhibition is the key to the blood pressure effects of these drugs.

Another family of enzyme inhibitors, the decarboxylase inhibitors, appeared to offer another promising approach to the treatment of hypertension. Since decarboxylase is an enzyme essential to the production of norepinephrine, epinephrine, serotonin, and other biologically important amines from their amino acid precursors, it was thought that inhibiting this enzyme might block production of these amines. However, it now appears that even very potent decarboxylase inhibitors do not make any appreciable dent in tissue levels of these amines, and that to do so would require that the enzyme be inhibited by nearly 100 percent.

Studies now underway at NHI are evaluating compounds that inhibit dopamine-beta-oxidase, an enzyme that acts one step further along the norepinephrine-epinephrine production line than does decarboxylase. Several compounds which inhibit this enzyme effectively block norepinephrine production in vitro, but their effectiveness is still to be evaluated in laboratory animals.

COAGULATION AND HEART DISEASE

Most of the crippling and lethal effects of atherosclerosis result from the obstruction of vital blood channels by blood clots rather than by the atherosclerotic deposits themselves. The atherosclerotic lesion provides a roughened surface conducive to the formation of clots. Further, the high serum lipid levels usually associated with atherosclerosis appear to increase the tendency of the blood to clot and also to impede its clot-dissolving mechanisms. The clot forming on an atherosclerotic plaque may further obstruct flow through the already narrowed channel, or it may break free, eventually to block some smaller vessel somewhere downstream. There is also evidence that blood clots may themselves give rise to some types of atherosclerotic lesions.

The increased clotting tendency frequently observed in atherosclerosis may be due in part to elevated serum levels of two phospholipids that appear to be active in promoting the formation of clots. These two lipids, phosphatidyl ethanolamine and phosphatidyl serine, appear to be able to mimic the clot-accelerating action of blood platelets, and may even be the active principle of platelets. NHI grantees have shown that serum levels of these two clot-promoting substances are two to three times as high in patients with coronary heart disease as in normal subjects. They also found that diets low in saturated fats could reduce serum levels of these two phospholipids by as much as 25 percent; and that diets low in saturated fats and also containing a higher proportion of polyunsaturated fat could reduce these levels by an additional 35 to 55 percent.

Anticoagulants, which reduce the clotting tendency of the blood, have proved to be highly effective both in the treatment and in the prevention of heart attacks. Long-term studies have amassed substantial evidence that continuous anticoagulant therapy after first heart attacks significantly reduces the incidence of recurrent attacks. When administered as a prophylactic measure to patients with angina pectoris, anticoagulants apparently reduce the risk of first attacks. Anticoagulants also appear to reduce the severity of heart muscle damage and to improve the rate of survival when used during the acute phase of heart attacks.

In a recent review of 200 cases of myocardial infarction (heart attack), the patients were classified as "bad risk patients" if they had had a previous history of breathing difficulty on slight exertion, heart failure, shock, or abnormalities of heart rhythm; as "good risk patients" if they had no history of such abnormalities.

Among the good risk patients who received anticoagulant therapy, the mortality rate was 10.4 percent; among the good risk patients receiving no anticoagulant therapy, it was 29.4 percent. Among the bad risk patients, the mortality rate was 39.3 percent for those receiving anticoagulant therapy classified as adequate; 48 percent for those receiving anticoagulant therapy classified as clinically inadequate; and a whopping 80 percent for those receiving no anticoagulants.

Although anticoagulants act primarly by preventing the formation of clots, there is also evidence that they may also potentiate the clot-dissolving action of fibrinolytic agents. Studies by NHI grantees revealed that, when supplemented with heparin, fibrinolytic drugs would dissolve clots in doses that were completely ineffective in the absence of heparin.

Another promising approach to the treatment of thromboembolic complications so often attending atherosclerosis is fibrinolysis. This involves the use of agents to dissolve clots already formed, either by acting directly on the clot or by activating the body's own clot-dissolving mechanisms.

The latter appears to be the more promising approach. This is because a blood clot already contains the seeds of its own destruction in the form of plasminogen, which was trapped inside the clot as it formed. Plasminogen is inactive, but is the precursor of plasmin, the substance that actually dissolves the clot. In fibrinolysis, it is thought, plasminogen activator from the blood accumulates on the fibrin surface of the clot and proceeds to convert the entrapped plasminogen to plasmin. The plasmin then breaks down the clot from within by digesting its fibrin.

A number of studies indicate that drugs which activate this clot-dissolving mechanism are effective against clots less than 72 hours old. It appears that older clots become organized and prevent the activator from reaching the plasminogen inside the clot.

Fibrinolytic agents have been used by NHI grantees during the acute phase of heart attacks and as an adjunct to the surgical removal of clots obstructing large blood vessels. They have reported varying degrees of clinical success. However, present techniques are not adequate for the accurate assessment of the clinical effects of these drugs. Fibrinolysis is a highly promising, rapidly expanding field. Until improved techniques for evaluating these drugs become available, it will probably continue to be a controversial one.

RHEUMATIC FEVER

The most significant advance scored against rheumatic fever and rheumatic heart disease during the past few years was the development of the fluorescent antibody technique for the rapid identification of the strep germ responsible for rheumatic fever. The technique is simple, reliable, and rapid. By reducing the time required for accurate diagnosis of type A beta hemolytic strep infections, the technique makes possible the rapid initiation of antibiotic therapy and thus minimizes the danger that rheumatic fever may subsequently develop. The technique has repeatedly proven its worth in field trials. At present, the heart disease control program is training personnel of State and local health departments in the use of the technique to insure its widest possible application.

The heart disease control program has also cooperated with the Chicago Board of Health and other local agencies in the establishment of a rheumatic fever registry for that city. Presently, about 5,149 cases are registered, estimated to comprise about 50 percent of the total cases of rheumatic fever among children and young adults. Of these, 3,445 have received free drugs (sulfadiazine or penicillin) as a prophylactic measure against recurrent attacks. Electronic computation techniques are used to keep track of drug distribution to the subjects and to verify their keeping scheduled medical appointments. Missed appointments result in the initiation of prompt follow-up action. The feasibility and worth of such a registry is amply demonstrated by the low incidence of recurrent rheumatic fever attacks since 1956. Recurrences among those on the register have averaged 10 per 1,000 per year; recurrences among those not registered are estimated to run nearly three times as high.

A study of the prevalence of strep germs and strep infection was carried out among 400 children from three Madison Wis. schools. Throat swabs were taken twice a month from December through June for 3 years. The highest incidence of strep germs found at any one time was 30.2 percent, predominantly type A beta hemolytic strep. The incidence of these germs was nearly twice as high among children with tonsils as among those without tonsils. The study also showed that, although type A strep was usually the culprit in most of the infections with clinical manifestations, these germs could also exist almost continuously in the throats of some children without producing any clinical symptoms.

When rheumatic fever strikes, it has been generally accepted that prompt treatment with anti-inflammatory agents such as prednisone or aspirin will reduce the probability of heart damage or at least reduce its severity. However, studies by NHI grantees suggest that anti-inflammatory treatment neither eradicates the carditis accompanying rheumatic fever nor does it significantly reduce the incidence of residual heart disease.

They point out that most patients who present themselves for treatment early in rheumatic fever ususally do so because of severe joint involvement. The benign course that usually attends anti-inflammatory therapy in such cases is not primarily the result of the therapy, but of the tendency of rheumatic to spare the heart when it hits the joints hard. Conversely, the heart is likely to be hit hardest by rheumatic fever when the evidence of joint involvement is slight, whether or not the patient receives prompt anti-inflammatory therapy.

In fact, other studies by these scientists indicate that such therapy may actually be detrimental if initiated in the absence of clinical signs of rheumatic activity. For these studies the scientists selected rheumatic fever patients who had completed a course of anti-inflammatory therapy 1 month earlier. None showed any clinical signs of rheumatic activity at the beginning of the study. Two groups of patients were given an additional 2-week course of therapy with prednistone or aspirin; the control group received no therapy. After cessation of therapy, 9 out of the 29 receiving prednisone and 1 of the 29 receiving aspirin exhibited flareups of rheumatic activity. None of the controls did. The authors conclude that rheumatic activity may accumulate under therapeutic suppression to produce this so-called posttherapeutic rebound.

SURGERY

Hypothermia is frequently employed in heart surgery, especially in those open-heart procedures requiring long periods of heart-lung bypass. Hypothermia reduces the metabolic demands of the tissues for oxygen. This reduces the amount of blood that must be pumped by the heart-lung machine, protects the heart against fibrillation, and also makes it possible to stop the heart safely for longer periods.

Profound hypothermia is often required when the circulation must be interrupted for the long periods often required for the repair of complex cardiac abnormalities. Many surgeons, concerned that the very low temperatures used might seriously interfere with the ability of hemoglobin in red blood cells to give up its oxygen to the tissues, have advocated that the blood be deliberately rendered more acidic to facilitate the process. However, acidosis may also produce many harmful effects on the circulation.

Studies by NHI scientists evaluated the effects of acidosis in dogs during profound hypothermia. Their studies indicated that altering the acidity of the blood had no effect on oxygen consumption. Their finding suggest, in fact, that whether hemoglobin is able to give up its oxygen readily may be of little importance under these circumstances, since oxygen may be supplied to the tissues solely from the oxygen dissolved in plasma. They conclude that since acidosis serves no useful purpose and may have harmful effects on the heart, it should not be induced in clinical surgery.

Other NHI studies evaluated the effectiveness of various techniques used to protect the heart during prolonged periods of arrest. The studies showed that the heart could safely withstand longer periods of arrest and regained normal function more rapidly when external cooling of the heart was supplemented by intermittently perfusing the coronary arteries with cold, oxygenated blood. Cooling the heart apparently reduced its metabolic requirements enough so that these could be adequately met by the perfusions. The techniques also protected against the possibly harmful effects of uneven cooling or a rise in temperature once hypothermia had been initiated.

Anoxic arrest, in which the heart is stilled by intermittently clamping the aorta, allows the heart to be stopped safely for longer periods with less subsequent depression of heart function than does cardiac arrest induced with such chemical agents as acetylcholine or potassium citrate. However, NIH grantees report that cardiac arrest by means of electrically induced fibrillation may be even more effective.

The technique, previously tested in dogs, has since been employed clinically. The periods of arrest ranged from 1 minute to 117 minutes, with an average of 30.5 minutes. The scientists report that resusciation after arrest was easy and that the period of arrest had no adverse effects on subsequent heart performance, provided that during the period of arrest the heart chambers were protected against overdistention and the coronary arteries were perfused with adequate quantities of blood.

NHI grantees also report the successful use of highly flexible tubing for cardiac catheterization procedures. By taking advantage of the patient's own blood flow to help position the catheter, manipulation of the catheter under fluoroscopic guidance is frequently unnecessary. They report that the tubing can be inserted into veins through a needle or into arteries through a previously inserted piece of plastic tubing. The technique is safe, easily learned, and highly useful. It provides a simple means for measuring pulmonary artery pressure that may be carried out in the office or ward during routine cardiovascular workups. The scientists report that the tubing can also be maneuvered readily into such relatively inaccessible vessels as the internal carotid, coronary, or renal arteries to measure blood pressures or to withdraw blood samples.

Although the day when a victim of heart disease might be able to trade in his damaged heart for an artificial model might still be a long way off, work on such artificial hearts has progressed substantially. NHI grantees have developed two types of artificial heart, both suitable for implantation within the chest cavity. Fifteen of these have been implanted in dogs whose own hearts had been removed. Some of these animals survived for 14 to 20 hours. The grantees report that the artificial hearts were able to maintain normal mean blood pressure and produced no hemorrhage or pulmonary edema; however, they did produce a considerable degree of mechanical damage to blood elements.

A mass field trial using taped heart sounds to detect unsuspected heart disease has been carried out among 33,026 Chicago schoolchildren. The tapes were evaluated by two cardiologists, and "suspicious" cases recalled for more thorough examination. Approximately 1 in 7 of those recalled were found to have heart disease. The scientists report that this procedure is quick, reliable, and reduces the number of children requiring direct physical examination for the detection of possible heart disease by more than 98 percent.

Epidemiological programs of the National Heart Institute

Epidemiology, stated simply, is the application of the scientific method to the study of population groups. The problem to be solved is defined, and facts are gathered and appraised. Then, one or more hypotheses are formulated and tested. Finally, conclusions are drawn and preventive methods are designed and applied.

Epidemiological studies of the National Heart Institute are examining heart disease in relation to one or more possible causative factors. The most common factors studied, in addition to age and sex, are: (1) geographic location, (2) diet, (3) physical activity, (4) smoking, obesity, and overweight, and (5) heredity.

Geographic location

Since 1912, records have shown a statistical increase in heart disease. It is generally believed that this is due to increased accuracy in diagnosis and reporting. One authority estimates that less than 15 percent of this increase is an actual increase in the disease.

Recent grantee studies have revealed important geographic differences in death rates. In the United States, the rate varies between States. One study has shown that even in different areas of New York City, the age-adjusted death rates range from 249 to 689 per 100,000 population.

A study conducted by the heart disease control program surveyed 163 metropolitan areas and 116 nonmetropolitan areas in the United States. They found the low death-rate areas to be in the Western Plains with a few such areas in the Middle South. The high-rate areas are near the east coast, with some along the gulf, the Great Lakes, and the west coast. These differences suggest that some elements within rural and urban environments may also be linked to the disease. Investigations are proceeding to identify which factors may be most important in this relationship. Mineral content of drinking waters and the composition of soils in different geographic areas are additional factors now receiving attention.

Diet

Much of the evidence linking dietary fat to the development of atherosclerosis in humans has been derived from epidemiological studies. Such studies have produced strong evidence against cholesterol and saturated fats to make them prime suspects as chief dietary contributors to atherosclerosis.

Worldwide epidemiological studies on diet have shown that coronary artery disease is not a major public health problem in large areas of the world where there is a scarce food supply. Serum cholesterol levels of people in these areas are much lower than those of Americans and, perhaps significantly, their dietary intake of saturated fats is also low.

Among the factors studied throughout the world have been total dietary fat, saturated versus unsaturated fats, and the protein-fat-carbohydrate ratio of the diet.

A proposal now under consideration would provide funds for studies that will determine the feasibility of undertaking a large-scale study to identify the relationship between the kinds of fat in the diet and the mortality from coronary heart disease.

Physical activity

Although there is some conflict of opinion, most epidemiologists agree that physical activity is related to the incidence of mortality in heart disease.

Population studies on physical activity have shown that the highest incidence of coronary artery disease occurs in the occupational groups which have the least physical activity. The lowest incidence occurred in persons doing hard physical labor. Several studies are attempting to assess the role of physical activity in relation to the development of coronary heart disease.

Two recent studies are examining the records of college freshmen at Harvard University and the University of Pennsylvania during the years 1939 through 1946 and are assessing the mortality experience of this group. This followup study, using alumni records, permits the testing of certain hypotheses concerning physical fitness and other factors, in relation to cardiovascular disease.

Smoking, obesity, and overweight

Population studies at Framingham and other locations have linked cigarette smoking with an increased mortality in coronary artery disease.

The Heart Institute is also doing a followup study of 290,000 U.S. Government Life Insurance policyholders and their smoking habits. This study which began in 1953, is continuing and supports original findings of a strong association between cigarette smoking and lung cancer and also between cigarette smoking and coronary heart disease. A 63-percent excess mortality from coronary heart disease has been found to be present among individuals who have been cigarette smokers in contrast to those who did not smoke cigarettes or only smoked them occasionally.

It is often difficult to determine the difference between overweight due to obesity and that due to increased muscularity in many instances, and scientists often disagree about the extent to which obesity is related to heart disease. Generally it has been found that excessive overweight is associated with a higher mortality from coronary heart disease. In one recent study of longshoremen no correlation could be found between overweight and heart disease. Epidemiological studies have shown, however, that overweight associated with hypertension has a greater adverse effect on the incidence of arteriosclerosis than either factor alone.

Heredity

It has long been thought that a tendency toward coronary artery disease is hereditary and epidemiological studies are seeking to determine the importance of heredity in contrast to environmental influences in the development of this disease. For example, certain types of hypercholesterolemia tend to run in families, and recent studies have shown that there may be a definite genetic component that affects serum cholesterol levels.

In other recent studies epidemiologists are assessing mortality experiences in relation to hypertension and enlargement of the heart in a followup study based on previous records made in 1946 during a tuberculosis survey in Columbus, Ga. The subsequent experience of persons who had abnormal blood pressure or X-ray findings at that time is now being determined and observations in family members of these participants are underway to determine the familial relationship of hypertensive disease.

This and similar studies are uniting the geneticist and the epidemiologist in a new approach to the study of heart disease.

Every year, epidemiological studies conducted and supported by the National Heart Institute increase in number and scope. A collaborative research agreement has been undertaken to begin an epidemiological study of hypertension and coronary heart disease on defined segments of the adult population of Israel. The contrasting dietary patterns of segments of the population of Eastern and Western origin provide an important natural experiment in which the role of diet in cardiovascular disease can be studied. This longitudinal study of approximately 15,000 adults will provide data for comparison with studies made in the United States.

Epidemiological studies, although they have not conclusively revealed a single agent or factor that can be considered the cause of coronary heart disease, have shown that multiple factors, complex and interwoven, are involved. Further knowledge of the influences and interrelationships of these factors will define more precisely the role of each and will aid in outlining practical preventive programs that could lower the high incidence of mortality from this primary health problem for the more developed countries of the world today.

Cardiovascular aspects of biomedical engineering

The cardiovascular aspects of and interest in the burgeoning field of biomedical engineering, biomedical electronics, and related activities are both extensive and intensive. The field is one, of course, of opportunity and potential for all the life sciences. Within this framework, the mission of the National Heart Institute, for research and other programs aimed at increasing cardiovascular knowledge and its application, has enabled interest and support for development and participation in projects and areas of benefit to the heart field.

In both broad and specific terms, bioengineering (used here to comprise a spectrum of disciplines and fields as suggested above) has contributed much to the resources against heart disease. Cardiovascular surgery, for example, has progressed to its present dramatic attainments with the aid of many developments involving bioengineering: protheses such as heart valves and grafts, heart-lung machines, hypothermia devices, heart catheterization, complex monitoring and analyzer equipment, anesthesiology techniques, and a variety of other instrumentation.

The range, in fact, of cardiovascular aspects of the field concerns all or almost all research disciplines and, as well, those involved in the application of knowledge. The range also is one extending from broad areas of activity, such as that of a university engaging in a biomedical electronics program, to specific projects to develop measures useful in finding unsuspected heart disease, such as one for helping diagnose heart disease in schoolchildren through use of tape recordings of their heart sounds.

Many of the programs of the National Heart Institute, and of the heart disease control program funded by the heart appropriation, involve bioengineering directly or indirectly. Many research grant projects, for example, include as an integral part of the investigative undertaking instrumentation complements which have been developed in recent years to aid medical and biological research in securing ever more exacting and precise measurements and other observations. A number of heart research projects grants, furthermore, provide support for research where electronic methods or bioengineering constitute the main body of the project. An example here is support for new instrumentation research involving electronics systems for long-period, continous recording of electrocardiographs on tape by a portable, miniature electrocardiocorder and subsequent rapid analysis of the resulting large volume of data by means of another instrument.

In the field of heart disease control, the heart program is currently developing and aiding in work to evolve analysis, evaluation, and transmission of electrocardiograms through use of electronic data computers and telephone reception and transmission of the information. The heart disease control program is also participating in such other bioengineering activities as the previously mentioned use of heart sounds recordings to find heart disease in children and as the further development of techniques, equipment, and other facets of the fluorescent antibody streptococal identification test which promises much for physician diagnosis of strep infections.

A further idea of the extent of cardiovascular interest and the potentials for it of the bioengineering field may be gained from a glance at a few heart related activities and developments on the current scene:

Telemetering instruments to study the heart, bringing more accurate information about its physiology and state in health and in disease.

Development of cardiac pacemakers: such as one tiny electronic device implanted inside the body to help regulate a faltering heartbeat; and another small enough to be carried in a shirt pocket.

Interdisciplinary biomedical electronics programs such as at a university where, on the program's research side, projects are underway to develop radiotelemetering systems for transmitting stimuli and recording physiological data.

Automatic time lapse electrocardiography for long-term monitoring of the fetal heart.

Electronic electrocardiograph monitor and transmission instruments combining, for example, a receiver, transmitter, ECG tape recorder, and oscilloscope; and capable of transmitting electrocardiograms from magnetic tape records or an ECG machine from physician to physician.

A method for detecting left-to-right heart shunts in congenital heart defects without the necessity of drawing blood samples but through use of a platinized electrode.

Electronic and mechanical devices for cardiac massage to aid patients suffering cardiac arrest or heart stoppage.

A listing of cardiovascular biomedical electronics instruments and other apparatuses presented via exhibits at the 1961 American Heart Association showed some 16 bioengineering concerns exhibiting hundreds of heart and blood vessel electronic and mechanical aids for researchers and physicians.

DIETARY SURVEYS

Much of the evidence linking dietary fat to atherosclerosis in humans has been derived from epidemiological studies. These compare carefully selected population groups which differ sharply in their mortality from atherosclerosis, but which are as similar as possible in all other respects except for the dietary factors under study. In this way, it is hoped, the specific dietary factor or factors responsible for the mortality difference can be effectively isolated from among the many other variables that might also operate in atherosclerosis.

Such studies have accumulated enough impressive evidence against cholesterol and saturated fats to make them prime suspects as the chief dietary contributors to atherosclerosis. Conversely, a large body of evidence has accumulated to suggest that unsaturated fats, especially such polyunsaturated fatty acids as linolenic and arachidonic acids, lower serum cholesterol levels; and it has been postulated that they may confer some measure of protection against atherosclerosis.

Some examples:

South and east African Negroes, who subsist on a diet very low in total fat, animal fat, and protein, have a much lower mortality from heart disease than do south African white settlers, whose dietary patterns—and mortality from heart diseases—are similar to those of Americans. Atherosclerosis appears to be almost nonexistent among young Negroes of these groups, but does occur in middle-aged and older Negroes. The disease is much less severe and its lesions contain less lipid than in the case of Americans. Most striking, however, is the extreme rarity of myocardial infarction ("heart attacks") and other cardiovascular disorders involving blood clots, even among those Negroes with atherosclerosis.

High-fat diets appear to increase the tendency of the blood to clot and also to impede the fibrinolytic mechanisms by which the body dissolves clots. Thus the low-fat diet of the African Negro may confer protection against heart disease not only by retarding the development of atherosclerosis but also by preventing the thromboembolic complications usually attending the disease and often the immediate cause of its crippling and lethal effects.

Many other studies on selected populations from all over the world have revealed the same striking associations between diet (especially dietary fat), serum cholesterol levels, and relative proneness or immunity to atherosclerosis. Among the factors studied have been total dietary fat, animal (saturated) versus vegetable (chiefly unsaturated) fat, and the protein-fat-carbohydrate ratio of the diet.

That dietary factors, not genetic factors, may be primarily responsible for the differing degrees of susceptibility to atherosclerosis exhibited by these populations has been suggested by other studies. These compared population groups from countries with a low incidence of heart disease with groups of the same racial origin who had migrated to this country and adopted "Westernized" dietary patterns. The studies have shown that the low mortality from heart disease apparently enjoyed by some of the natives of Italy, Japan, Africa, and other countries is not shared by their racial counterparts in America who succumb to heart disease with about the same distressing frequency as to other Americans.

If diet is largely responsible for high death rates from cardiovascular disease, then the possibility exists that changing our habitual dietary patterns might reduce our presently better-than-even odds of dying from one of this family of diseases.

A proposal now under consideration involves a series of grant-supported feasibility studies to determine whether it is possible and desirable to undertake a large-scale study to elucidate precisely the relationship between the kind of fat in the diet and mortality from coronary heart disease. For these preliminary studies a dietary regimen has been tentatively worked out which involves a large reduction of the proportion of animal fat in the diet and the substitution of unsaturated vegetable oils. The regimen would be simple enough to be followed easily in the average home, and, hopefully, palatable enough to be followed voluntarily by large groups for long periods of time. The projected feasibility studies are preliminary to a large-scale study proposing, if such a study is found possible, to determine whether such a diet will reduce mortality from heart disease; and, if so, whether large segments of our population will voluntarily accept a basic change in their dietary pattern.

ANIMAL STUDIES

Studies on the effects of diet on atherosclerosis in laboratory animals are complicated by the fact that few commonly used laboratory animals develop the disease spontaneously. In most, atherosclerosis can be induced experimentally only by diets extremely high in cholesterol, and frequently this diet must be augmented by drugs that interfere with normal fat metabolism, or by surgically produced hypertension. The lesions produced may differ from those of humans, and are rendered somewhat suspect by the drastic methods required to produce them.

Primate colonies, such as those established this year, should contribute greatly toward the solution of this problem. Primates, physiologically, are very similar to man. Furthermore, many primates appear to develop atherosclerosis spontaneously, with lesions closely resembling those of the disease in humans. Thus these animals should be ideal for more extensive, more detailed laboratory studies of important leads uncovered by epidemiological research.

One such study, comparing Kenya baboons with baboons from a primate colony, has shown that both groups develop atheroscerosis spontaneously even though their average serum cholesterol level (114 milligrams percent) is only about half that of humans (225 milligrams percent). However, their serum also showed a decided preponderance of low-density lipoproteins, which transport most of the cholesterol in serum; and, in humans, such a preponderance is associated with proneness to atherosclerosis. The relationships observed between the development of atherosclerosis in baboon and such factors as age, sex, and diet also closely paralleled those observed in epidemiological studies on human populations.

STUDIES ON FAT METABOLISM

Studies in this area have been aimed at clarifying the mechanisms governing the absorption, synthesis, transport, and breakdown of fatty substances in the body. If, as many believe, atherosclerosis is a disease caused primarily by abnormal lipid metabolism, basic studies of this sort are the ones most likely to extend medical control over atherosclerosis.

CHOLESTEROL

The cholesterol consumed in the normal human diet is probably the least important source of the cholesterol of serum. The major source is the liver, which readily synthesizes cholesterol from acetate, a 2-carbon building block arising from the metabolism of protein and carbohydrate as well as from fat.

The liver can produce enough cholesterol to maintain excessive serum cholesterol even when the diet contains none. In fact, excessive serum cholesterol levels have been induced in animals by diets containing little fat of any kind, but containing excessive calories derived from carbohydrates. Other studies have indicated that the total caloric content of the diet may be at least as important a factor in its effects on serum cholesterol as the amount and kinds of fat it contains.

Studies on the mechanisms regulating cholesterol production by the liver indicate that cholesterol synthesis is controlled by a double feedback system. Feedback, one of the most important mechanisms for regulating the synthesis of any compound by the body, prevents enzyme systems from glutting the market with their particular product, almost literally, by drowning the enzyme system in its own surplus.

If a substance is made at a faster rate than it can be used or gotten rid of, the surplus that accumulates interferes with further production, usually by inhibiting an enzyme involved in some earlier step in the production line. The surplus product is often so similar in chemical structure to the substance ordinarily processed by that enzyme (called the substrate) that the enzyme cannot discriminate between the two. Thus the product is able to compete with the substrate for the enzyme's active site. The enzyme cannot act on the surplus product perched on its active site; but, as long as it is there, the enzyme also cannot act on its normal substrate. As more and more surplus product accumulates, it increasingly crowds out the enzyme's normal substrate and slows further production.

A surplus of cholesterol apparently inhibits two earlier steps in the complex sequence of reactions by which cholesterol is made from acetate. A diet high in cholesterol can almost completely suppress cholesterol synthesis in many laboratory animals, but this inhibition appears to be less pronounced in man. Cholesterol synthesis appears to account for 60–75 percent of the serum cholesterol in humans, even when their diet is high in cholesterol.

Another feedback mechanism affecting cholesterol synthesis involves bile acids, the major pathway for cholesterol excretion. The accumulation of bile acids blocks some step in their production from cholesterol. If this cholesterol cannot be diverted into other metabolic channels, it piles up, inhibiting further cholesterol synthesis.

A number of hormones and drugs affect serum cholesterol levels primarily by affecting the relative rates of cholesterol synthesis and excretion. For example, thyroid hormones lower serum cholesterol even though they actually step up the rate of cholesterol synthesis. Serum cholesterol falls because these hormones cause an even sharper increase in the production and excretion of bile acids.

Serum cholesterol levels may also be rather precisely determined by genetic mechanisms, other factors being equal. One study on these genetic factors compared serum cholesterol levels in a group of identical twins (who presumably carry the same genes) with these levels in a similar group of fraternal twins, who are as genetically distinct as any two children of the same parents. Although the group as a whole exhibited a wide range of serum cholesterol patterns, when each pair of twins was considered separately, the serum cholesterol pattern of one identical twin always corresponded very closely with that of the other. The differences in serum cholesterol patterns between fraternal twins were much greater.

The mechanisms by which saturated fats act to increase serum cholesterol and by which unsaturated fats act to reduce it are still obscure. Unsaturated fats actually appear to increase cholesterol synthesis. Like the thyroid hormones they might overcompensate by stepping up bile acid excretion, but proof for such a mechanism is lacking. Over 70 percent of serum cholesterol is combined with fatty acids (cholesterol esters). One hypothesis suggests that esters in which cholesterol is combined with unsaturated fatty acids may be more readily taken up from the circulation by the tissues.

Unsaturated fats will not lower serum cholesterol when superimposed on a diet high in saturated fats. They must be substituted for these saturated fats. The balance between unsaturated and saturated fats in diets designed to reduce serum cholesterol appears to be a very delicate one. One such diet, containing 30 percent of its calories as unsaturated fats and 8 percent as saturated fats reduced serum cholesterol levels by 15 percent. However, the addition of only 1 percent of saturated fat to this diet completely eliminated its cholesterol-lowering effect.

LIPOPROTEINS

Lipoproteins are large fat-protein molecular complexes synthesized by the liver. They appear to be the transport vehicles for about 95 percent of the total serum lipids. (The other 5 percent is free fatty acids, which are transported by albumin.) For convenience, lipoproteins are divided somewhat arbitrarily into two weight classes: high-density and low-density lipoproteins. Each class can carry any sort of lipid except free fatty acids; but, as it turns out, the low-density fraction usually carries the major portion of cholesterol and neutral fat (triglyceride) of serum.

The rate of lipoprotein synthesis and the ratio of high-density to low-density lipoproteins are affected by genetic, nutritional, and hormonal factors. It is still an open question whether the ratio of high-density to low-density lipoproteins affects the handling of fat by the body or whether the shoe is on the other foot, with the amount and kind of fat available determining the lipoprotein ratio. In any case, a preponderance of low-density lipoproteins is usually associated with high serum cholesterol and relative proneness to atherosclerosis, whereas a robust high-density fraction appears to confer some measure of protection against the disease.

The Yemenite Jews, who appear to be virtually free from athrosclerosis and heart disease, have a relative preponderance of high-density lipoproteins that appear to carry a large proportion of their serum cholesterol, which is low. When diabetic Yemenites were placed on the typical diabetic diet—high in fat and protein, low in carbohydrate—they tended to develop lipoprotein patterns similar to those of Europeans.

The immunity to atherosclerosis enjoyed by the Yemenites appears to reside more in their large high-density lipoprotein fraction than in their low serum cholesterol. This was suggested by studies comparing Yemenites with other Jews who had coronary heart disease but did not have high serum cholesterol levels. In fact, some of these had serum cholesterol levels as low as those of healthy Yemenites, but all of the coronary patients had much lower values for serum high-density lipoproteins.

The female sex hormones (estrogens) which protect the premenopausal woman against atherosclerosis do so primarily by increasing the relative amount of serum lipid carried by the high-density lipoproteins. It is also noteworthy that diets which reduce serum cholesterol levels also appear to reduce the proportion of low-density to high-density lipoproteins in many cases.

Tangier disease, a rare familial disorder of lipid storage discovered only last year, is providing unique opportunities to study the role of the two lipoprotein classes in human fat metabolism. The disorder is characterized by the accumulation of extremely large quantities of cholesterol in retucloendothelial tissues such as those of the tonsils, lymph nodes, liver, and spleen; by abnormally low serum cholesterol levels; and by the virtual absence of serum high-density lipoproteins. Tangier disease provides the first reported instances of a deficiency of this type of lipoprotein.

The clinical manifestations of Tangier disease indicate that high-density lipoproteins may be essential to the normal uptake of cholesterol by tissues and may also play a role in its esterification. Studies on this disorder are continuing at NIH, and, when correlated with similar studies on recently discovered patients who lack low-density lipoproteins, may help to clarify the roles played by the two lipoprotein classes in human fat metabolism.

THE ATHEROSCLEROTIC LESION

Other important studies have concentrated on the mechanisms by which the lipids of atherosclerotic lesions are deposited in the blood vessel wall. It has not yet been determined conclusively whether these lipids diffuse passively into the wall from the serum, are produced locally by the blood vessel tissues themselves, or are deposited at the site of mechanical injury or clot formation. Each of these theories has its stanch advocates and its supporting evidence. Too, there appears to be no natural law against all three processes getting their licks in at one stage of the disease or another.

The filtration theory holds that lipoproteins carrying cholesterol or other lipids diffuse passively into the arterial wall, become trapped in the maze of fibrous tissue, and gradually accumulate to form lesions.

Studies on the aortas of dogs with experimentally produced atherosclerosis disclosed a definite gradient of lipid deposition along the length of the aorta. Cholesterol deposition was highest in the ascending aorta and progressively less down its length in the early stages of atherosclerotic development. Aortic specimens studied later in the course of the disease revealed highest concentrations of cholesterol in the abdominal aorta. This is believed to be caused by the slower rate at which cholesterol leaves this site after diffusing passively into the arterial wall.

Autopsy studies on human aortas exhibiting a full range of atherosclerotic lesions have suggested that these lesions may develop as follows:

The first stage is the appearance of fatty streaks, composed of lipids synthesized and extruded by cells of the arterial wall. These fatty streaks were found in aortas from all autopsy subjects over 3 years old, but their rate of development appeared to be most rapid about the time of puberty. The fatty streaks were followed about 20 years later by the appearance of fibrous plaques. The fatty streaks appeared to be reversible, but the fibrosis did not.

Other studies indicate that some atherosclerotic lesions may arise from the degeneration and organization of blood clots forming on the inner wall of the blood vessel. The lipid found in such lesions may be derived in part from lipid-rich blood platelets trapped in the clot. Other findings suggest that when some portion of the inner wall of a blood vessel is deprived of an adequate oxygen supply by such factors as local injury or blood-clot formation, there is an increased uptake of lipoproteins by that portion of the vessel.

NHI SUPPORT IN THIS FIELD

Research exploring the subject of diet in relation to atherosclerosis and coronary heart disease has been productive, as the findings cited above indicate. The growing fund of factual knowledge that is taking shape in this field has resulted in great measure from the research support provided by the National Heart Institute. Literally hundreds of grant-aided research studies in this country and others abroad have contributed basic, clinical, and epidemiological findings. Investigations in the disciplines of biochemistry, nutrition, and pathology have been particularly fruitful. Many obscure areas and many unsolved problems remain, nonetheless. While some relationships have been clearly demonstrated (e.g., that the fat content of the diet can influence serum cholesterol levels), others have not as yet been proved (e.g., that high cholesterol levels are causally related to more rapid progression of atherosclerosis). Past results suggest that continued investigation will eventually define the precise role of diet in arteriosclerosis and coronary disease.

Diet studies are, of course, only one facet of Heart Institute-supported research aimed at discovering the basic etiology of heart attacks. The number and variety of factors implicated in atherosclerosis and its consequences, and the strong relationships that some of these seem to have, make it unlikely that this disease has a single cause. It appears that there may be a multiple etiology, and that the development of atherosclerosis and coronary disease may be owing to the combined or accumulated effects of a diversity of factors. Among factors which may play significant roles in relation to coronary disease are heredity, hypertension, lipid metabolism, emotional stress, age, smoking, physical activity, blood vessel trauma, vascular anatomy, sex, and obesity. The National Heart Institute supports investigations relating to all of these areas and also supports many studies, ranging from fundamental work in cardiovascular physiology to clinical trials of techniques and therapeutics, from which new information of significance constantly develops.

PRIMATE CENTERS

The primate research center program of the National Heart Institute is directed toward meeting the widely recognized need for suitable facilities for conducting research on subhuman primates. This program, which has developed as a result of the active interest of the National Advisory Heart Council and the encouragement and support of the Congress, has made substantial progress. Three primate research centers are now underway and promise to add appreciably to the Nation's research potential when completed.

A primate research center as conceived under this program is an organizational entity providing an optimal environment wherein resident and visiting scientists, representing a breadth of disciplines, may actively pursue research in order to advance all possible areas of knowledge relating to the biological characteristics of the primate throughout its entire lifespan. Such a center, in spirit and in fact, must be a major research resource facility to meet regional and national needs. Grants have been made for establishment of centers meeting these specifications in Oregon, Washington, and Wisconsin.

Oregon regional primate research center

The Heart Institute's primate center program was inaugurated in April 1960 with the awarding of grants to the Medical Research Foundation of Oregon for the construction and initial operation of a regional primate research center at Portland. Supplemental grants have since been made for additional construction at the center, for laboratory equipment, and for operation of the facility during fiscal year 1962.

The new facility, which will provide for a research program based on a colony of 400 monkeys, is being built on a large tract of land about 10 miles west of downtown Portland. The Medical Research Foundation of Oregon has administrative responsibility for execution of the grants. The University of Oregon provides the academic environment within which the center will operate.

Construction of the facility has now reached the stage of 90 percent completion. The rather unique outdoor-indoor animal colony buildings have been finished for several months and some research investigations involving the rhesus monkey are already underway. Dedication of the fully operational facility is scheduled for May 1962. The center will then offer an excellent opportunity to investigate primates in depth throughout the life cycle and to correlate the efforts of the many scientific disciplines involved.

Investigators utilizing the center will work toward the definition of such vital processes as are involved in heredity and in the origin, specialization, and functional mechanisms of living cells and organ systems in the primate in health and disease. Some of the areas of investigation include physiology and biochemistry of the fetus and newborn, fetal skeletal biochemistry and growth, congenital anomalies, and cardiovascular physiology and pathology. Information gained from these studies will contribute to the understanding and control of human disease.

Washington regional primate research center

In May 1961 grants were made to the University of Washington for the construction and initial operation of a regional primate research center to be located on the university campus in Seattle. Architectural planning is now in progress, and it is anticipated that construction will begin by late summer or early fall of 1962.

Research at the University of Washington has utilized primates for some time although in necessarily limited fashion because of lack of facilities. The new primate research center will provide a specialized environment for investigations on the biological characteristics of the rhesus macaque and other species of monkey. It will serve as a facility for university faculty members using primates in medical, biological, and psychological research. The center will also emphasize the training of visiting scientists in primate research techniques and primate care. Further, it will also serve as a center for development and dissemination of new information about primate research.

Among key investigations to be carried on at the center will be studies in neurophysiology and electrophysiology, gastrointestinal physiology, skeletal and dental development, physiological psychology, and obesity and dietary factors in cardiovascular disease.

Wisconsin regional primate research center

Grants were also awarded in May 1961 to the University of Wisconsin for the construction and operation of a regional primate research center at Madison.

The University of Wisconsin has for many years been interested in and supported primate research. The primate laboratory of its department of psychology has been one of the largest in the country designed to study psychological and physiological problems of primates. Many of the techniques now used in primate maintenance and research, particularly research with infants, were developed at the laboratory.

The new primate research center building will be a four-story-and-basement building adjacent to the present primate laboratory, on a site in the campus extension area. Architectural planning for the center is proceeding well with designs scheduled for completion in late spring 1962. Actual construction is expected to begin by early fall.

The Wisconsin center initially will provide a facility to conduct integrated research programs in the fields of neuroanatomy, physiology, biochemistry, and psychology, with special emphasis on problems that can be investigated in newborn and infant rhesus monkeys. An extensive breeding program will be undertaken to provide a constant supply of young animals. Long-term holding facilities will be built to permit study of the more than 25-year lifespan of the rhesus monkey.

Among investigations that will receive emphasis in the new center are studies on postnatal development of the primate brain, hormonal factors in reproductive processes, biochemical factors associated with mental retardation, and variables influencing the development of normal and abnormal affectional systems.

Recent developments

Grants for three additional primate research centers are projected for fiscal year 1962. One application, from Emory University in Atlanta, Ga., has received favorable review by the National Advisory Heart Council and is currently subject to negotiation prior to the awarding of funds.

The grants to Emory University, if and when made, will be for the construction and initial operation of a primate research center designed primarily for multidisciplinary study of the chimpanzee. Proposed site of the center is a 21-acre tract of land on the university campus. Establishment of this center would assure continuation and further development under optimum conditions of the psychobiological research of the Yerkes Laboratories of Primate Biology, Inc., owned by Emory University and presently located in Orange Park, Fla.

During the 30 years the Yerkes Laboratories have been in existence, they have achieved notable success in solving practical problems of care, breeding, and efficient handling in experimentation and in accumulating knowledge about the basic physiological, behavioral, and structural characteristics of the chimpanzee. The Orange Park colony has grown from a dozen or so animals to about 70, ranging in age from newborn to 39 years.

Areas of research emphasis at the new center, when established, would include studies on (1) the relation of infant growth and experience to behavior in later life; (2) physical, physiological, and psychological attributes of aged primates: (3) perceptual and cognitive functions; (4) brain functions; (5) comparative studies with monkeys and with other anthropoids; and (6) effects of unusual environments and intense stimulation.

In addition to the center projected for Emory University, the program being developed by the National Advisory Heart Council with the help of its consultants includes the initiation in fiscal 1962 of two other regional centers for primate research. One center would be located in New England, probably in the Boston area, and the other in the South, in the vicinity of New Orleans.

Overall national needs in the primate field have also received the attention of the Heart Council. Among them, for example, is the question of the potentials of a primate conditioning center for the purpose of studying the subhuman primate in terms of (1) procurement, including capture, transportation, and general handling; (2) conditioning and maintaining healthy colonies; and (3) identifying and evaluating the suitability of various species, as well as specific genetic strains, for particular medical research purposes.

Far too little is known about the subhuman primate as an experimental animal. A special center devoted to studies of the aforementioned nature would be of great assistance to the regional centers and a stimulus for the extension of research to many different species of primates, as well as improving the quality of primate research in laboratories throughout the country. This type of center would also aid in solving the national problem of dwindling supply through the development of captive breeding colonies and the eventual distribution of animals uniquely suitable for immediate use in biomedical research.

GENETICS RESEARCH

The National Heart Institute's interest in genetics research accrues from the known but puzzling relationship between heredity and heart disease. Heredity has long been implicated as a causal factor—along with such others as diet, stress, sex, and exercise—in the four major types of cardiovascular disease; i.e., atherosclerosis, hypertension, rheumatic heart disease, and congenital defects of the cardiovascular system. In any given cardiovascular disease, however, the precise nature of the genetic defect (or defects) involved, as well as how, when, and in whom it interacts with environmental factors to produce overt disease, are largely within the realm of the unknown.

The hereditary elements are the genes, arranged linearly along 23 pairs of chromosomes. Abnormalities in the number, size, or configuration of chromosomes can lead to gross inherited abnormalities since large numbers of genes are affected. The genes are arranged in pairs called alleles, one gene being derived from the father and the other from the mother. When two or more alleles governing a trait become relatively common in a population, the genetic system is said to be polymorphic. The polymorphisms introduce a considerable amount of inherited normal variation in human populations, and in some cases are related to disease susceptibility. Less commonly, a disease is the expression of a single allele (pair of genes); such a disease is said to be dominant if only one gene is involved, or recessive if both genes are required.

The problem of identifying a genetic influence is very difficult; similar types of congenital heart defects, for example, may be the result of heredity in one patient, environmental changes during fetal life in another, or both factors acting in concert in still a third patient. Even when heredity is singled out as the primary cause of a disease (as in some of the rarer cardiovascular disorders), the gene or genes involved, the nature of their derangement, and the mechanisms whereby this is manifested as structural and/or biochemical deviation in the whole organism is, again, unknown.

Some inherited abnormalities are amenable to the curative or palliative efforts of physicians. Many congenital heart defects for example, some of them inherited, are totally corrected by modern surgical techniques. And certain inborn errors of metabolism that can lead eventually to mental retardation are being detected in newborn infants by means of simple biochemical tests. Early diagnosis enables the institution of special diets and other forms of therapy before irreversible brain damage occurs.

Such therapeutic advances are heartening and further efforts in this direction are deserving of continued support. It is our fervent hope, however, that prevention rather than therapy will be the ultimate solution to the clinical control of inheritable diseases. As matters stand with our present state of knowledge the only preventive measure widely advocated is the precaution against exposure to excessive radiation levels. Only is such a clear cut hereditary pattern established that two individuals can be strongly advised against bearing children. Further reference to therapy and prevention is, perhaps, premature, especially with regard to those diseases strongly influenced by hereditiy, since an individual's environment is easier to manipulate than his heredity.

More basic information is needed concerning the relative roles of heredity versus environmental factors in producing various disease states. Much of this information will be obtained from studies of family histories spanning several generations and from long-term epidemiological studies involving large population groups. Investigations of a more fundamental nature, probing the very foundations of life, are providing useful information on the hereditary material itself.

Applied and basic studies in the field of genetics, embracing a broad spectrum of biomedical research disciplines, are conducted intramurally or supported by research grant funds. Some representative examples of these are described below.

NHI GRANT SUPPORTED STUDIES IN GENETICS

Until recently, "giant satellites," which appear to be large, separated chunks of certain chromosomes, had been found only in patients with congenital abnormalities. NHI grantees recently reported their observation of giant satellites in clinically normal subjects from two different families. Such giant satellites appear, then, to be a structural chromosomal variant within the range of normality. They may actually be a size variant of normal satellites, or they may represent minor translocations of chromosomal material. In the latter case, the giant satellites might be compatible with normal development, but also conducive to abnormalities of the offspring. The abnormalities may arise through the possession of excess or deficient quantities of genetic material presumably carried in the translocated giant satellites. The grantees also speculate that, since giant satellites are transmitted with the chromosomes carrying them, giant satellites may serve as chromosomal markers. Demonstration of a linkage between them and known genetic traits may then localize specific genes on specific chromosomes. This would be an important step toward human chromosome mapping.

This same group of scientists recently published a review article on recent developments in the field of human cytogenetics. Because much of the information is recently acquired and the communication of it has been widely scattered, a review such as this, of the relations of peculiar chromosomes to mental, to sexual, and to other physical abnormalities, represents a meaningful and useful synthesis of biologic and medical information.

Another grant-aided study has provided evidence that essential hypertension is a distinct genetic and biochemical entity rather than an extreme of normal variation. In this study, prehypertensive medical students (whose parents were hypertensive) were characterized by an inability to destroy the blood vessel-constricting properties of angiotensin which was injected into their circulation.

Experiments investigating the combined effects of heredity and diet on the production of atherosclerosis in three breeds of pigeons have shown that a fatty diet produced the severest lesions in the White Carneau pigeon. This pigeon, which develops atherosclerosis spontaneously while on a normal grain diet, also developed lesions which more closely resembled those found in humans. Dietary-induced lesions were least severe in Racing Homers, an atherosclerosis-resistant breed, and were intermediate in Auto-sexing Kings, a breed genetically intermediate between White Carneaus and Racing Homers. Serum cholesterol levels were similar in all three breeds.

A survey of serum cholesterol levels in 56 pairs of twins ranging in age from 5 to 63 years, suggest that, despite great variation in cholesterol levels between persons of all ages, the levels observed during youth may be quite precisely predetermined by genetic mechanisms.

Recent reports of families in whom a normally present lipoprotein fraction was absent or present only in decreased amounts have suggested that there is a simple genetic basis for the production of the protein fraction of these lipoproteins. Even more recently, NHI grantees reported the familial occurrence of a qualitative variant of serum beta-lipoprotein, thus adding to the evidence for genetic control of the production of lipoproteins. If the protein involved in a lipoprotein complex is under direct genetic control, detection of additional variations due to molecular changes in the protein may be expected.

INTRAMURAL GENETICS RESEARCH

Intramurally, several basic and applied studies bearing on the field of genetics, reported to this body last year, are being continued.

The basic studies involve experiments directed toward establishing how hereditary "information" coded into the genetic chromosomal material in cells is translated by the metabolic machinery into structures and properties that characterize individuals. The studies being carried out in the Heart Institute at the basic level employ such organisms as bacteria and bacterial viruses which reproduce very quickly and on which, consequently, large amounts of statistics can be obtained in a relatively short time. Strains of such organisms are exposed to various agents which cause mutations, or changes in hereditary potential. The results of such hereditary changes are expressed in terms of the changes in such properties as resistance to heat, or the ability to carry out specific biochemical reactions.

It is assumed at the present time that hereditary "information" is used by cells as a set of directions for the production of specific protein molecules which, in turn, perform the necessary functions of enzyme catalysis, hormonal action, and of furnishing structural material for building tissues. A single minute change in the genetic code, therefore, is expected to lead to a minute, but important, change in the structure of a corresponding protein molecule. The understanding of the relationships between the "genetic code" and the "protein code" is under active study.

Recent findings suggest, however, that regardless of which one of the two "codes" determines the primary structure of an enzyme, it does not determine the complete structure, required for enzymatic activity, of the molecule. NHI scientists reported that ribonuclease, after being subjected to a chemical shakeup severe enough to disrupt its normal spherical shape and to eliminate its enzymatic activity, is able to regain both properties simultaneously under suitable chemical conditions. This finding indicates that, in many cases, the amino acide sequence alone may be enough to determine the secondary and tertiary structure of an enzyme. This is good news to protein chemists interested in enzyme synthesis. Protein chains of predetermined length and amino acid sequence can be synthesized in the laboratory, but the task of molding these chains into the proper configuration to confer enzymatic activity upon them appeared to pose far more formidable problems.

The genetic aspects of Tangier disease, first reported last year, are still being studied. The disease is a rare inherited disorder of lipid transport and storage discovered in certain residents of Tangier Island, Va. It appears that individuals with the complete syndrome might be unable to make high-density lipoproteins; or they may make lipoprotein molecules whose protein moiety is defective in some way. Since lipoproteins are the carrier vehicles for all of the cholesterol in serum, either of these circumstances could interfere with the normal transport and absorption of cholesterol.

SMOKING AND CARDIOVASCULAR DISEASE

The possible role of smoking as a factor in the development of cardiovascular disease has been a subject of investigation for many years. While the various studies carried out have established a number of facts as to the effects of smoking on the heart and circulatory system, knowledge is still very incomplete. Consequently, the question of whether smoking bears a causal relationship to heart disease remains controversial.

There is general agreement that smoking produces transient effects on the heart and blood vessels and that nicotine is the most important element in producing these effects. In most persons the effects of smoking include an elevation in blood pressure, an increase in the pulse rate, a flattening of the T wave in the electrocardiogram, and constriction of the peripheral blood vessels, indicated by a decrease of the skin temperature of the extremities. There is considerable variation among individuals in their physiological response. It has been found that the content of nicotine of a standard cigarette must be reduced more than 50 percent before no vascular effects are produced. Contrary to a common impression, the constriction of blood vessels that occurs with smoking is not prevented by ingestion of alcohol.

Substantial evidence exists showing that smoking has seriously deleterious effects in peripheral vascular disease such as thromboangiitis obliterans, and recent studies have indicated that this may be due to tobacco sensitivity or allergy. The exact nature and the net effect of smoking on the heart have not at the present time been adequately defined, however, and whether smoking may have a pathogenetic relationship to heart disease is not now known.

While physiological evidence showing that smoking causes heart disease has not been found as yet, impressive data have been accumulated strengthening the statistical association between smoking and mortality from coronary heart disease. Reporting on 44 months of followup of a large number of men, Hammond and Horn found that the death rate due to coronary disease in men with a history of regular cigarette smoking was 70 percent higher than for men who had not smoked. Buechley et al., in a followup study of California longshoremen, found that the coronary artery disease mortality rate of those smoking a pack or more of cigarettes a day was about twice the rate of those who smoked fewer or none at all. Dorn, reporting on the National Institutes of

Health study of U.S. Government life insurance policy holding veterans, found that the death rate from coronary heart disease was 63 percent higher among regular smokers than among nonsmokers.

These findings on mortality rates have recently been paralleled by findings on incidence. Zukel et al., reporting on a study in which the Public Health Service participated, of males 35 years of age and older in a six county area of North Dakota, found that heavy cigarette smokers had an incidence of myocardial infarction double that of the nonsmokers. Doyle et al., reporting last October on the combined experience of the Albany, N.Y., heart disease study of male civil servants and the Heart Institute's Framingham, Mass., heart disease study of a community population, found a threefold increased incidence of myocardial infarction in cigarette smokers as compared to nonsmokers, reformed cigarette smokers, and pipe and cigar smokers. No association of smoking was found, however, with the incidence of angina pectoris.

The statistical association of heavy cigarette smoking with coronary disease is clear. The mechanism whereby heavy cigarette smoking increases the incidence and mortality of coronary heart disease is obscure, however. No presently available evidence indicates a direct causal relationship; hence the definite statistical association suggests that cigarette smoking may be a factor contributory to the progression of coronary heart disease. Cigarette smoking may perhaps aggravate the condition or its complications or act to provoke manifestation from a latent state. More knowledge is necessary before the true relationship is understood.

CEREBROVASCULAR DISEASE AND STROKES

Cerebrovascular disease is a medical problem that spans the research interests of two of the National Institutes of Health. Because it is brain disease, it is a major concern of the Neurology Institute: because the blood vessels are heavily involved, it is of much interest to the Heart Institute. Coordination and unification of the dual interests have been advanced this past year through the establishment of a Joint Council Subcommittee of the National Advisory Councils of the two Institutes.

Many of the Heart Institute's conducted and supported investigations concerned with atherosclerosis and hypertension are part of the research attack on cerebrovascular disease. Studies of the broad problems of pathogenesis and disease processes and mechanisms are included as are studies of more specific areas such as coagulation, fibronolysis, hormones, and diet. There are also special activities in the cerebrovascular area.

A cooperative study presently in progress on cerebral arterial insufficiency, in which some 16 geographically dispersed investigative teams are participating, is of special significance. In the past few years it has become recognized that atherosclerotic disease of extracranial arteries supplying the brain can produce significant cerebral symptoms. It has also been shown that surgical treatment of well-defined atherosclerotic lesions in such arteries located in the neck and upper chest can dramatically restore adequate cerebral blood flow. In the cooperative study, patients with symptoms of cerebral insufficiency are studied by angiography and other diagnostic methods to determine whether impeded blood flow in extracranial arteries is the principal cause of the symptoms. Those patients who are found to have occlusion of extracranial arteries and are considered likely to benefit from surgery are treated by the most appropriate surgical procedure to remove or bypass the impediment to blood flow. All of these patients are intensively studied before and after treatment under a standard protocol and the data obtained are being pooled in a central registry at Baylor University for analysis. The study is expected to meet the need for better criteria by which to select patients suitable for surgical treatment: provide knowledge of the efforts of such arterial surgery on cerebral blood flow; and provide patient evaluation data for determining the clinical benefits of such surgery and, perhaps, what the optimum form of treatment may be.

The remarkable promise of surgical treatment of patients with cerebral arterial insufficiency caused by blockage of extracranial arteries is indicated in the results reported by an NHI-grant-aided surgical research team. Examination by arteriography of 895 patients, most of whom had neurologic symptoms of cerebral arterial insufficiency, revealed extracranial arterial occlusion in 361. Of the 326 of these patients who were treated by arterial reconstructive surgery, results 7 to 14 days after operation showed that 170 were asymptomatic, 61 improved, 64 unchanged, 8 worse, and 22 had died.

The patch-graft technique reported last year has increased the safety and successful use of endarterectomy (the direct surgical removal from an artery of atherosclerotic deposits, clots, or other lesions obstructing blood flow) to restore circulation in the extracranial arteries supplying the brain. The technique solves the problem of constriction of the artery at the site of the incision during the healing process, which formerly limited use of endarterectomy to larger vessels. Following removal of the arterial obstruction through a longitudinal incision made in the artery, a Dacron patch is inserted at the incision site and the wound edges are sutured to the patch rather than to one another.

A method of studying the blood circulation of the brain in man by using radioactive-labeled red blood cells has been developed by an Institute grantee. Following injection of the cells into the carotid arteries and subsequent sampling of blood every second from the jugular bulbs, dilution curves are plotted. The method may prove sensitive for detecting certain cerebrovascular diseases, as curves for patients with cerebrovascular lesions and arteriosclerosis were found to be quite different from the uniform and characteristic curves of control cases. In recent studies of cerebral circulation in 34 healthy males, no correlation was found between cardiac output and cerebral bloodflow or between the latter and the age of the subjects.

In other grantee studies, a technique for calculating bloodflow in the carotid artery of dogs within 5-percent accuracy, by using a collimator (scintillation detector divided into two detecting parts) for recording radioactivity, has been reported. The technique may offer a practical method for scanning bloodflow on the two sides of the neck in humans without the need for surgical exposure of the neck vessels.

The problems of communication between scientist and scientist and between scientists, physicians, and other health professions, appear to be impediments to the progress of medical research and to the application of new knowledge. With a view to assisting in the communication of cerebrovascular information, the Joint Council Subcommittee of the Neurology and Heart Institute Advisory Councils has prepared a trial issue of a Cerebrovascular Bibliography to explore the need, the content, and the format of an effective periodical bibliography in this field. It is planned to publish an issue every 4 months for a limited period of time. During its developmental period, the bibliography is being distributed to a limited number of leading scientists and teachers, who have agreed to advise the subcommittee concerning it. If the publication proves valuable, it will be made generally available to the scientific community. The trial bibliography, which covers the world literature in the cerebrovascular field, was prepared with the cooperation and assistance of the National Library of Medicine and utilizes a mechanized listing index system that makes possible rapid publication.

Complementing the efforts being made in research, the application of knowledge to benefit the stroke patient is also being extended. Grants and technical assistance provided to States under the heart disease control program are helping to accelerate community activities in this field. More than a dozen States are now allocating part of their grant funds for cerebrovascular disease programs. Areas of activity and emphasis vary in different States but commonly include professional education, demonstration and research projects, and methods evaluation.

In one State, for example, a program of restorative services for stroke patients has been developed that involves participation of the State health department, heart association, medical schools, and medical societies. Hundreds of public health nurses have been trained in proper bed positioning and exercises necessary to restore function in stroke patients. They can thus bring recommended rehabilitation procedures to patients in their homes, with the result that much disability is prevented.

Another development of particular interest, a national stroke conference to be held in 6 to 9 months, is being planned by four cooperating agencies—the American Medical Association, the American Heart Association, the Office of Vocational Rehabilitation, and the heart disease control program. The conference will be concerned with rehabilitation, management, and prevention of strokes, and be attended by 100 to 150 persons representing all disciplines involved in treatment of the stroke patient and all geographic sections of the country. The conference is to be followed by a much larger stroke congress to be held immediately preceding a clinical session of the American Medical Association. It is hoped that the impact of the conference and of the congress on those attending, and on others who learn of its proceedings, will generate greater demand for services for stroke patients and for demonstration programs that will inform the layman, educate the professional, and develop more resources for treatment of stroke patients.

STATE CONTROL PROGRAMS

In 1961, the Congress made an appropriation of $3½ million for grants to the States for the development and improvement of programs in heart disease control. This appropriation was increased in the current year to $5 million.

States use the formula grant (with 100 percent matching funds) for the administration of their statewide heart programs; laboratory services for heart disease diagnosis; clinics and case-finding activities; nursing services, particularly at community levels; statistical services for heart disease surveys and studies; and professional and public education programs. Nearly 50 percent of the funds support community level heart disease control activities.

Last year all States demonstrated and tested the new fluorescent antibody technique for the rapid identification of the streptococcus believed to cause rheumatic fever; this tool is making it possible for the infection to be diagnosed by physicians in a matter of hours, rather than days. Prophylaxis programs to prevent recurrences of rheumatic fever were carried on in most sections of the country. In 12 States, a significant portion of the grant was used to develop better services for the restoration of stroke victims to self-care and useful lives. Many jurisdictions started projects to bring together and improve all community services, including nursing, to benefit heart patients.

States have generally devoted the increase in the current year to the following activities: development and conduct of training programs in the fluorescent antibody method for technicians from local laboratories, to spread this rapid diagnostic tool to communities within States; training public health nurses in restorative techniques for stroke patients in "Strike Back at Stroke" campaigns; and the building of solid, continuing State heart programs through the recruitment and training of professional persons at State and local levels. Many States have extended the laboratory programs to include tests for lytic agents and are cooperating with the Institute's standardization and reference laboratory at Atlanta to insure comparability of blood cholesterol and other determinations relating to heart disease. Also important in this year's expenditure of the State control funds is better planning for nutrition and obesity control activities; several States are engaged in lay nutrition education as well as in controlled nutrition studies. Ten States are now cooperating in long-term community studies of coronary heart disease; they are conducting carefully controlled investigations into the extent to which stress, smoking, diet, and trace elements, and other environmental causes may be associated with the onset of heart attacks.

Of the $3.5 million appropriated for State control programs last year, all but 6.1 percent was expended or obligated. The total funds available from all sources in the States for heart disease control reached a high last year—nearly $12 million.

Preliminary review of State use of the formula grant this year shows that 85.2 percent of the funds available for the first 6 months were requested and programed by the States. It is expected that the total utilization will increase to over 90 percent by the end of the year.

A primary goal in this program is the encouragement of States in building permanent, meaningful heart disease control activities into their programs. Greater emphasis on the planning process will, it is felt, lead to better programs and thus to an improved lot for heart patients. Toward this goal a subcommittee of the Heart Disease Control Advisory Committee, consisting of State officials, was appointed to help States improve their planning for utilization of the heart grant-in-aid. To date, their proposals have been tested in four States and have been favorably received.

BIOENGINEERING

Mr. FOGARTY. Dr. Rusk, as you know, was before us last year, and he or the gentleman with him showed us a vessel stapler.

He had been able to refine it and make it better than the original product that came out of Russia.

What are you doing in the field of bioengineering?

Dr. Shannon. Mr. Fogarty, that is the field that is assigned to the Division of General Medical Sciences under Dr. Halsey Hunt. I can describe very briefly what is being done.

As a result of conferences held over the past 12 months, we now have coming to us, or in the process of coming to us, I would say, five or six fairly broad research grant applications for support of bioengineering and instrument development, or a combination of the two, that look toward the creation of regional resources, rather than specific institutional resources.

For example, I have in mind one that will join together Hopkins, Maryland, University of Pennsylvania, and, I think, one of the New York schools.

The problem there is that it will be our responsibility to convince the National Advisory Research Facilities Council to give preferential treatment to construction grants, because these cannot go forward without construction funds.

I think, on the other hand, if we have very good research grant proposals——

Mr. Fogarty. Is this special stapler a good example to use?

Dr. Shannon. I do not look at that as being the type of thing I would hope would develop from——

Mr. Fogarty. He said they were able to do some things with this that the human hands could not do.

Dr. Shannon. Well, I think that is perfectly true, sir. And I do not mean to minimize the importance of this as an isolated invention. But I do not look upon this as a great achievement. I have in mind some of our needs for instrumentation, the absence of which precludes our really uncovering some vital interrelationships in the normal development and functioning of the body, in the absence of which we find it very difficult to understand certain aspects of disease.

Mr. Fogarty. You do not think much of this stapler?

Dr. Shannon. Oh, I do.

Mr. Fogarty. Dr. Rusk thought it was a real good example. He told us how they were able to get it from Russia and this contractor was interested and spent of his own money to refine it, and make a better one than was built in Russia. They said that they were able to save some lives because of it, because it was impossible for the surgeon to do some of the things that this could do.

Dr. Shannon. Well, I would not quarrel with the importance of the instrument in specific disease situations. I would say, though, that I think the development is more important as evidence of Russian recognition that both biological investigation and current medicine have reached the point where it can make more effective use of certain engineering skills that have been developed outside the medical field.

So I would say that this development, to my mind, is important because it demonstrates the sucecssful interplay of biology and engineering rather than because of the instrument that came out of it. This is a matter of opinion.

STATISTICS ON SUCCESS OF OPENHEART SURGERY

Mr. FOGARTY. What about openheart surgery, Doctor? I suppose it all depends on what kind of a problem it is and how old the person is and so forth. But some people go to the trouble of looking up the statistics of survival and then decide to go on with a restricted life rather than taking a chance. Then there are others who take the chance, based on the best evidence they had from their doctor, and don't recover. And then the family may say that if they knew the real statistics that they would not have taken a chance on the operation.

Dr. SHANNON. Mr. Fogarty, I had the benefit of reading the letter you received——

Mr. FOGARTY. I was not referring just to this particular letter, but I know of other people who feel the same.

This letter, I thought, was very well written and it gives a specific example.

I thought I would give it to you because I do not like to have snap judgments made on the basis of a few cases.

Dr. SHANNON. No, sir.

Mr. FOGARTY. I thought we would give you a chance to answer it if you want to, or put a statement in the record about it.

Dr. SHANNON. Well, we can do it either way, sir.

The point I would make is that the writer of the letter implied that statistical data on the hazards involved are not known. I would say these are very well known.

Mr. FOGARTY. In what way? Where are they?

Dr. SHANNON. In numerous articles that have been published in the past 2 years since open heart surgery has become practical.

But I might point out that Dr. Terry was for a number of years chief of the clinical services of the Heart Institute, and he is in a very good position to appraise whether, in his opinion, the average surgeon with this capability is or is not aware of the hazards that he faces.

Mr. FOGARTY. This particular person, Dr. Terry, raised the question of the mortality rate in open-heart surgery and the lack of statistics made available to patients on the probable success of surgery and chances of surviving without surgery.

But I think that this is so important that, rather than have you consider it offhand, I would rather give you the letter.

If what he says is right, I think we should be doing a better job in getting better dissemination of accurate information in this field. It is a well written letter.

DEVELOPMENTS IN HEART SURGERY

Dr. TERRY. Well, rather than comment on that letter directly, I would like to make some general comments with regard to cardiac surgery.

In the first place, I think that one should bear in mind that when you are talking about cardiac surgery, one has to consider what the surgery is being done for. There are many types of surgery done upon the heart, which are well established, almost routine procedures, today.

During the early years of development of this technique, for instance, in repair of congenital defects of the heart, such as openings in the wall between various chambers and this sort of thing—certainly, the mortality was quite high. During this time, as the surgical technique was developing, the supportive techniques—supportive, but absolutely essential, such as the pump oxygenator—were also being developed. And there were many deaths back in those days of surgery which were due to surgical errors because we had not developed the technique to the stage that we have today.

And there were some that were due to the fact that the pump oxygenators which we were using at that time were not satisfactory.

Mr. FOGARTY. Several have been developed since then, though, have they not?

Dr. TERRY. Yes, sir. That was the point I was about to make.

Generally speaking, I think we can say today, from the standpoint of our pump oxygenators, that they are very effective and very safe, and we are not running into many of the technical difficulties that we ran into.

Having that ironed out, the extension of surgical technique has gone along quite well, and, speaking of repairs of congenital defects, if one looks at the life expectancy of the individual, both in terms of morbidity and mortality, and thinks in terms of the mortality when the operation is done by well-trained surgical groups today, I do not think there is any question but that we have made tremendous advances and that we are doing very, very fine work in many centers throughout this country today.

Now, in other types of diseases of the heart, such as diseases of the coronary vessels, where some persons believe that we may be successful one day in going in and removing obstructions immediately after they have occurred, or where we have demonstrated marked thickening and narrowing of the coronary arteries by arteriosclerosis, that we can go in before a myocardial infarction, or a coronary occlusion has taken place and remove this.

I think, very obviously at this stage of the game, with this sort of development that we are feeling our way, and I do not think we know today—there has been very interesting and, I think, progressive work done in this direction. But on the other hand, it certainly remains to be seen whether this is a preferable method of treatment.

I think one must anticipate that as surgery advances into new fields of endeavor, there are obviously going to be more problems encountered than a later time after you are more sophisticated and more experienced in terms of selecting the cases that are the best operative risks and in terms of the exact details of surgical techniques.

I can see how any person who has lost a member of his family might be considerably disillusioned and upset over this particular circumstance. On the other hand, I think that, overall, we have made such tremendous advances in this direction that I think it is one of the great annals in modern medical history.

COSTS OF HEART SURGERY

Mr. **Fogarty**. Well, I think we are making great progress, but what about in the area of congenital heart defects in children? It is a very expensive operation, is it not?

Dr. **Terry**. Yes, sir, it is expensive.

Mr. **Fogarty**. I think we asked somebody 2 or 3 years ago. In some areas it was $2,000 to $3,000. How in the world is the average working person going to be able to afford to pay for an operation like that? What does the fellow with four or five kids do, making just an average salary?

Mr. **Kelly**. I might say with respect to another part of the department that, I think that the Children's Bureau will be able to testify that these costs have come down since this program was inaugurated on a fairly large scale; and that there is a significant amount of crippled children's grant funds being used for this kind of program.

Mr. **Fogarty**. If the program was five times that amount, it would not take care of all the children that need it.

Every once in a while I get letters asking for help and I send them on to the heart association or to the director of health in the State who handles these children's funds, and they tell me they do not have the money.

So what do you do then?

Dr. **Terry**. I do not know the answer to that general question, Mr. Fogarty. Certainly it is an expensive procedure.

QUALIFIED SURGEONS FOR OPEN HEART WORK

Mr. **Fogarty**. Open-heart surgery is getting better every year; is it not?

Dr. **Terry**. Yes, sir, I do not think there is any question about it.

Not only that, but there are many more groups, teams, in the country each year that are thoroughly qualified to do good work in this area.

Mr. **Fogarty**. But we still need more trained people?

Dr. **Terry**. I do not think there is any doubt but that we need more trained personnel.

I think another thing we need to do is be careful, as we develop these teams, that we give them all the support they need to do the fine work which they are capable of doing. Because one could, in terms of trying to get something going in an area, try to move too rapidly, and even though you have a very fine cardiac surgeon, unless he has a supporting team around him, he cannot do his best work.

And therefore I think it is very important that we do train and train well, and give these people the support they need.

UNMET NEEDS IN HEART RESEARCH

Mr. **Fogarty**. Doctor, I for one am not satisfied with the progress that is being made in this area. I think we ought to be training more people, and I think we ought to be building more facilities, and I think we ought to be spending more money on research. That is my opinion.

Now, I am going to ask you to give me just an overall statement. What do you think are the most important unmet needs of your Institute. If we decide to give you some more money, in what areas do you think it should be used?

FACILITIES

Dr. Knutti. Mr. Fogarty, I think that the real technical problems are dependent upon two major problems, without the solution of which it is going to be very difficult to advance. And one of these is the space in which to do research work and to train people.

Mr. Fogarty. You mean you do not have space out there at the Institutes?

Dr. Knutti. I was thinking of the overall situation in the country.

Mr. Fogarty. Throughout the country?

Dr. Knutti. Yes, sir.

Mr. Fogarty. What about where you are? I notice you are building another building for the Cancer Institute. How about you people?

Dr. Knutti. We still have home Heart Institute staff who are not on the reservation located in rented buildings in the Bethesda area.

Mr. Fogarty. We have one bill that authorizes $50 million for health facilities. We amended it last year to increase the authorization from $30 million to $50 million.

Mr. Laird. Just 1 year.

Mr. Kelly. Just through fiscal year 1963. It is up for consideration as a part of——

Dr. Terry. This is a part of H.R. 4999, a 3-year extension, of $50 million.

Mr. Laird. We have only $30 million this year.

Dr. Terry. That is right.

Mr. Kelly. In the Community Health Services and Facilities Act it was raised from $30 million to $50 million just through fiscal year 1963.

Mr. Fogarty. So that is only for 1963, unless we pass this other bill that is in the same committee now.

But that is one of the principal drawbacks—lack of facilities.

What is the next one?

MANPOWER

Dr. Knutti. The other one is a subject to which Dr. Shannon spoke the other day, and that is the manpower situation.

Mr. Fogarty. Well, we will have that report in a couple of weeks.

Dr. Knutti. But we can go ahead much more rapidly if we have the brains to do the work and the space in which they can do their work.

At the present time, as we visit the medical schools in this country, we find in many of our best institutions deplorable lacks of laboratory space. And this, I think, is one of the most important items in the development of not only the heart program but all of the rest of biomedical research.

Mr. Fogarty. Is there any other point you want to make before I stop my questions?

Dr. **Knutti.** The only thing I would say is, if we do have the men and the space we are not going to have any trouble getting ideas and finding problems, because there are plenty of them. And as one problem emerges and facets of it develop, other interesting and important leads appear. So that, at least at this stage of history, it is an almost endless chain of possibilities, if we have proper facilities with which to do it.

Mr. **Fogarty.** Do you think if we had the proper facilities and the necessary manpower and sufficient funds to spend in the area of research, that these expenditures would yield substantial returns to the national interest?

Dr. **Knutti.** I certainly do.

Mr. **Fogarty.** Mr. Marshall.

ALLOCATION OF GRANT-IN-AID FUNDS FOR HEART DISEASE CONTROL

Mr. **Marshall.** I notice that on page 190 of your justifications that you have allocations of grant-in-aid funds for heart disease control. I note that you allocated $5 million in 1962, and you estimate that you will allocate the same amount under this budget in 1963. Why does my State of Minnesota have $500 less than the estimated amount used in 1962?

Dr. **Knutti.** Sir, I cannot answer that specifically for your State. As you know, these funds are allocated on a formula basis. Certain States, because of the demands of their own programs, or their own program interest, vary their own programs from year to year so that they do not put as much, or they may put more money, into this particular effort.

We can find out why Minnesota is getting less. I would suspect that it has something to do with Minnesota's own plans to spend this money.

Mr. **Marshall.** Would you mind providing that, reviewing your statement and putting the correct information in, if it needs correcting, in the record?

Dr. **Knutti.** Glad to, sir.

(The requested information follows:)

Allocation to State of Minnesota

Allocation of grant-in-aid funds to States is based on the individual State's proportion of the national population (U.S. Census) weighted inversely by the State's per capita income (U.S. Department of Commerce, annual figures). In the latest per capita income figures, on which the allocations for 1963 are based, the per capita income for Minnesota rose slightly over the previous year. Under the formula distribution, this caused the Minnesota allocation for 1963 to drop slightly in comparison with the 1962 allocation.

RELATIONSHIP OF CHOLESTEROL TO HEART DISEASE

Mr. **Marshall.** Do you have any evidence that the consumption of dairy products contributes to failures of the circulatory system, or any other phase of heart disease?

Dr. **Knutti.** Sir, I think this is in line with the statement that we made about diet and atherosclerosis in general. We just do not know the answers to this problem. We have no specific evidence that dairy products cause atherosclerosis.

We have some evidence that some of the types of fat that are in many naturally occurring fats, also in milk, may cause a rise in blood cholesterol. The significance of this to ultimate atherosclerosis, however, is the answer we must have before we can make any positive statements as to whether or not milk or meat or anything else causes this disease.

Mr. MARSHALL. How much progress have you made in the last year toward finding an answer to this question?

Dr. KNUTTI. Our epidemiologic studies have continued. They still point with suspicion toward this relationship between cholesterol and atherosclerosis. The progress that has been made in trying to solve this particular crucial experiment is one which is now being planned on the basis of six collaborating units scattered over the country who are preparing to do a study to determine whether it is feasible to alter the diets of certain human volunteers who would go into the study. The planning is at the stage now where we hope to be able to proceed to find out whether we can embark on a bigger study to prove this or disprove it, by getting human volunteers to go on special diets for long periods of time.

Mr. LAIRD. I would not be for giving you the money if you were just trying to prove it.

Dr. KNUTTI. Sir, I did not mean to say, "to prove it"; did I not add, "disprove"?

Mr. LAIRD. I thought the emphasis was on "prove."

RESEARCH PROBLEMS

Dr. SHANNON. Mr. Marshall, may I comment on this because I do not want us to hold up the expectation to you that we may have the answer next year.

The basic process that we are studying in the male actually begins in the twenties, begins to cause serious medical disability in the late forties, and really broad disability in the late fifties. We are studying an abberation of a perfectly normal process for handling fat and a series of fatlike substances.

And the problem here—let us get to the dairy products very specifically—is that most population groups that are heavy consumers of dairy products are also heavy consumers of calories and tend to be above, rather than below, weight. So that it is almost impossible to pull out of a large population group definitive data that will permit one to say that this particular factor is the cause of this particular end effect. One must realize that the process continues over a period of 20 to 30 years.

There are feasibility studies underway to determine whether or not it is possible to study this in American population groups. My own belief is that it is unlikely that it will be possible; that the answer to this will come, either by inference from the study of other population groups in comparison with Americans or by some device that will permit us to modify, over a long period of time, the fat metabolism of individuals in a controlled fashion, so that the groups studied can be smaller and the studies can be more definitive.

This is a process that is going on in all of us around this table at the present time. It becomes overt only if the atherosclerotic process happens to be in a critical spot, such as the coronary artery, or a cerebral vessel. An individual can go through his entire life and come up with vessels that are just riddled with the process, but because they happen to miss critical areas, he will give every appearance of health.

This is probably one of the most difficult problems we must address ourselves to, and I think it is one of these things that will only be solved by some sort of indirect approach that is not fully apparent at the present time.

Meanwhile, we have to do the best we can, because the problem is tremendously important. It takes many lives. It causes great disability. We just cannot walk away from it and say, "Well, we are sorry we do not have the sharp weapons to solve it now." We have to use the weapons we have, blunt as they are, and keep trying.

But I would not want us to go away and leave in you the hope and expectation that we might have the answer next year, because there is one thing that is certain—that is, we will not have it next year.

Mr. MARSHALL. Dr. Shannon, it may be that a few people, including myself, may be a little bit touchy or even irritated at the moment because we do have the surpluses of dairy products building up. Then, as we have discussed in these hearings, talk about the strontium 90 content has its effect upon milk consumption; and while it has been my observation that there has not been any more alarm expressed over the consumption of dairy products in this last 12 months, as far as cholesterol content is concerned, yet, for some reason or other, many people have pointed this finger at dairy products which some of us think is a bit unfair.

So we are hoping that the National Institutes of Health will come up with an answer on this particular subject.

I would like to say in this connection that if it does have an effect upon the blood cholesterol level, and there is some danger, the dairymen in this country, I am certain, want the facts of it. They do not want to cover it up. I think most of them object to the basis that some of these statements have been made upon incomplete information.

Dr. SHANNON. Yes, sir.

Mr. MARSHALL. And so we are very desirous that something may be done to develop definite facts.

FRAMINGHAM, MASS., STUDY

Mr. FOGARTY. There is one other question I did want to ask. You can supply it for the record, if you want to, about the study in Framingham, Mass.

Dr. KNUTTI. Yes, sir.

Mr. FOGARTY. Will you supply something for the record on how long the study has been going, what results, and plans for the future?

Dr. KNUTTI. Yes, sir.

(The requested information follows:)

FRAMINGHAM HEART DISEASE EPIDEMIOLOGY STUDY

The National Heart Institute is continuing its long-term study of a randomly selected cross section of residents in the community of Framingham, Mass. The study has three objectives: (1) To identify the characteristics which may be related to the development of coronary heart disease and hypertension; (2) to estimate the magnitude of the risk factors which may be associated with the development of these disorders; and (3) to test various existing hypotheses of causation.

Approximately 5,000 normal adults between the ages of 30 and 60 were given an initial physical examination during 1948–52, and are subsequently being reexamined at 2-year intervals. The examinations are extensive, and data are recorded on all items which medical science suspects may possibly be involved in development of heart disease. As time passes and persons participating in the study develop heart disease, the information previously obtained is analyzed to disclose factors present in those who develop a particular heart disease as compared with those who remain free of the disease. Reexaminations of the study population for the sixth and seventh biennial visits are presently underway.

REPORTED FINDINGS

Nearly 290 persons have developed coronary heart disease during the years of observation. The accumulation of additional cases of coronary heart disease during the last 2 years has made it possible to strengthen the findings in relation to certain factors which seem to be associated with a higher risk of developing coronary heart disease in this population.

The principal factors, other than age and sex, which have been shown to be associated with a high risk of developing coronary heart disease, are: (1) Increased levels of serum cholesterol; (2) increased levels of blood pressure; (3) the presence of left ventricular hypertrophy; (4) excessive cigarette smoking; (5) low vital capacity; (6) excessive weight; and (7) lessened physical activity.

RECENT DEVELOPMENTS

During the past year, a method has been developed to transfer the accumulated observations and measurements of the study for computer analyses. This will allow a more precise assessment of the influence of changes in risk which may develop over the years in relationship to changes in factors such as serum cholesterol or weight. Present findings, while significant, are based only on the relationship of risk to the factors as measured on the first examination.

The availability of the highly cooperative study population and its continuing followup—some of the volunteers have traveled across the United States for their biennial reexaminations—has made possible the addition of side studies which, in themselves, are contributing valuable data. A sufficient number of cases of cerebrovascular accident are accumulating to allow preliminary analyses of factors related to the development of cerebral thrombosis, a disease process of major importance in the aging population of the United States. The examination procedure has been modified to detect cerebrovascular abnormalities and it is anticipated that data in relation to this disorder will be of major importance as this study continues.

Some new studies in progress are: (1) A study of the relationship of rheumatoid arthritis to the development of coronary heart disease; (2) a study of the predictive value of several types of serum lipids in coronary heart disease; (3) a study of the relationship of hormones to the development of coronary heart disease; and (4) a study of the role of urinary infections in the development of high blood pressure. Other studies are contemplated or are already in planning stages.

In addition to the direct value of the Framingham findings to physicians in directing therapeutic regimens for patients, the Framingham study has also provided a model for epidemiological studies of coronary heart disease. Visits to the study project by investigators from the United States of America and foreign countries are increasing. Many of these visits are for the purpose of seeking advice regarding contemplated studies. This consultation and training function of the Framingham study is contributing importantly to the development of more refined epidemiological research in the cardiovascular diseases.

Scientific publications from the Framingham program during 1961 and those currently in press are:

Dawber, T. R. and Kannel, W. B.: Susceptibility to coronary heart disease. Mod. Conc. Cardiov. Dis. 30: 671–675, July 1961.

Dawber, T. R., Kannel, W. B., Pearson, G., and Shurtleff, D.: Assessment of diet in the Framingham study; methodology and preliminary observations. Health News 38: 4–6 (January) 1961.

Dawber, T. R., Pearson, G., Anderson, P., Mann, G. V., Kannel, W. B., Shurtleff, D., and McNamara, P.: Dietary assessment in the epidemiologic study of coronary heart disease; The Framingham Study. II. Reliability of measurement. (In Press.)

Doyle, J. T., Dawber, T. R., Kannel, W. B., Meslin, S., and Kahn, H. A.: Cigarette smoking and coronary heart disease; combined experience of the Albany and Framingham studies. (In Press.)

Kagan, A., Dawber, T. R., Kannel, W. B., and Revotskie, N.: The Framingham Study—a prospective study of coronary heart disease. (In Press.)

Kannel, W. B., Dawber, T. R., Kagan, A., Revotskie, N., and Stokes, J., III.: Factors of risk in the development of coronary heart disease—six year follow-up experience; the Framingham study. Ann. Intern. Med. 55: 33–50, July 1961.

Kannel, W. B., Kagan, A., Dawber, T. R., and Revotskie, N.: Implications of the epidemiology of coronary heart disease for the practicing physician—the Framingham study. (In Press.)

Mann, G. V., Pearson, G., Gordon, T., Dawber, T. R.: Diet and cardiovascular disease in the Framingham study. I. Measurement of dietary intake; appendix—detailed description of the Framingham composite table. (In Press.)

Mr. FOGARTY. Mr. Laird.

PRIMATE CENTERS

Mr. LAIRD. Doctor, in last year's hearings, we discussed with Dr. Watt the establishment of the primate center at the University of Oregon. What sort of progress has been made on that construction?

Dr. KNUTTI. Mr. Laird, that is 90 percent completed, and the dedication of the building is scheduled for the first week in May, I think—in 2 months. That is the last word I had of it, as of last week.

Mr. LAIRD. What is the status of the other centers?

Dr. KNUTTI. I understand, although I have not seen these personally, that the centers at Washington and Wisconsin are either under construction or the plans are about completed.

There are certain of these primate centers that had been deferred for negotiations, for one reason or another.

Among those are the one at New Orleans; and I understand just recently that they have employed a very competent program director. This is one that was held up for this purpose.

The center at Emory, which has been delayed for the same purpose, we understand now has a competent individual to head it.

There is another request on the books which will be reviewed by the council next month from Harvard. I think that is the status of the centers that have been discussed at previous hearings.

At the present time also, there is a study being made by the primate committee of the possibility of a conditioning center.

DEFINITION OF "REGIONAL IN NATURE"

Mr. LAIRD. Now, these centers are all regional in nature, is that correct?

Dr. KNUTTI. Yes, sir.

Mr. LAIRD. What do you mean by that? What do you mean by "regional in nature"?

That is the term that was used in the hearings that were conducted by the Interstate and Foreign Commerce Committee when the Public Health Service and this administration went on record to repeal section 433–A. They said they only wanted to continue the use of that kind of authorization on projects that were "regional in nature"; and they said that primate centers were a good example of "projects regional in nature."

Now, I would like to find out what that really means.

Dr. KNUTTI. Well, sir, I was not in on the original planning of this or its definition.

Mr. LAIRD. Maybe Dr. Shannon could explain this to me.

Dr. SHANNON. Mr. Laird, a regional center, for whatever purpose it is established, is one that, while it may be housed within the walls of the specific university and be administered by that university, is run and has programs developed to satisfy the needs of a number of adjacent or regionally localized universities, rather than to satisfy only the needs of the host institution itself.

Mr. LAIRD. Is that not true with all your programs?

Dr. SHANNON. No, sir.

EXAMPLES OF REGIONAL CENTERS

Mr. LAIRD. What about the McCardle Cancer Clinic in Madison? Would you not call that reigonal in nature?

Dr. SHANNON. No, sir. It is regional in nature from the standpoint of the availability of its resources for advice or patient care; but the resources that are placed at the disposal of the staff are to satisfy their needs rather than the needs of several other research institutions that may be geographically close.

We had a research grant request for the construction of one of these centers at Harvard. Now, the School of Public Health at Harvard has had a large program utilizing primates for the better part of 10 years, and they proposed the establishment of a primate center.

When we inquired into this proposal we found that the resources they requested were barely adequate to satisfy the needs of their local staff, leaving no facilities to satisfy the needs of the other institutions in the Boston area. We told them that if they wished to apply for a research facilities construction grant for Harvard University to satisfy their needs, we would be glad to entertain it, but we could not conceive of this as a regional center.

Another example, is the Oregon center. We have said from the beginning, that something less than 50 percent of the total resources shall be available to the scientists at Oregon, and a proportionately smaller percentage as the facility becomes larger. An advisory group will allocate space both to the University of Oregon and to other institutions who might apply for it, so that the Oregon group will not be in a position to allocate the total resources to themselves regardless——

Mr. LAIRD. Let us just take this one in Oregon.

Dr. SHANNON. Yes, sir.

Mr. LAIRD. You are putting one in Oregon, you are putting one in Washington.

Dr. SHANNON. Yes, sir.

Mr. LAIRD. These are regional in nature. What medical research institutions is the center at Washington going to serve that the one in Oregon cannot serve?

Dr. SHANNON. Well, actually, these are turning out to be national centers instead of regional centers because of the specific nature of the programs. They are emphasizing the psychological aspects of the use of primates for experimental work in Washington; whereas, in Oregon, they are emphasizing the surgical and medical aspects.

The resources of the two centers are different in terms of the type of colonies that will be maintained. In both cases only part of the services will be used by the local university.

This is something that originally caused the Heart Institute some trouble because when the Advisory Committee came up with these two centers in adjacent States, the staff of the Heart Institute pointed out that these could not be considered regional in the ordinary sense of the word and would not accept their advice until further staff work showed that the general programs of the two institutions would not duplicate each other, that they offer quite different opportunities, and that they provide a mechanism for the use of those facilities by a number of universities.

Mr. LAIRD. I am just trying to get clear in my own mind why the Department is so insistent on this language about keeping on a regional basis when, really, all you do is try to justify not putting them on a regional basis when you get to the Council.

Dr. SHANNON. Well, put it this way: Each of these primate centers is either of a regional or a national nature, in that it provides resources for investigators outside the host institution to conduct their search.

Mr. LAIRD. Well, I think you would have been better off to let section 433–A stay the way it was, instead of trying to monkey around with it; and I really mean "monkey" around with it.

SIGNIFICANCE OF CHOLESTEROL

Have you seen any of these ads that have been running in the newspapers, periodicals, over television, and in all the public relations media, which are giving advice to consumers to use the lower cost spread?

Dr. SHANNON. Yes, sir; I have.

Mr. LAIRD. As we go over the testimony that has been given before this committee during the period of the last 8 or 9 years—and I am now looking at the statements made by Dr. Watt and yourself last year on page 950 of the hearing record—and look at the medical literature on this particular question, it seems that all of the responsible medical scientists have been very conservative. But the advertising literature has been quite the opposite.

What are your comments on that?

Dr. SHANNON. Well, I would agree with that statement, Mr. Laird. I think that the medical literature has pointed out the difficulty of attempting to define, in a specific fashion, the cause of atherosclerosis and its consequences—cerebrovascular and coronary disease.

It has pointed out that it may be that the consumption of disproportionately large amounts of saturated fat is a causative factor influencing the development of atherosclerosis. On the other hand, the proponents of this point of view cannot give quantitative estimates on what constitutes overindulgence in saturated fats.

Other articles have indicated that the use of unsaturated fats, either alone or in conjunction with saturated fats, can cause a downward displacement in the level of cholesterol and can cause a change in the pattern of other lipids in the blood: but I do not believe that any of the articles that have appeared in the scientific literature claim that they have demonstrated that the unsaurated fats can, in a positive way, prevent the occurrence of cardiovascular disease due to atherosclerosis and coronary attack; nor do I believe that they claim to have developed a regimen that will specifically prevent these occurrences.

I think that the inferences are there. This exists as a working hypothesis but the experimental proof that this is, in fact, the case and the experimental validation of any given dietary regimen appears to me as lacking at this time.

HEART RESEARCH NEEDS

Mr. Laird. Since you have taken over as Director of the Heart Institute, what would you consider the greatest need in the area of heart research? Is it personnel, buildings; what is it?

Dr. Knutti. I think, sir, that this ties in with the discussion we had a little earlier about the need for facilities and individuals who are trained to work in these facilities, to proceed with the many problems that really need to be done before we are able to completely solve cardiovascular disease.

As far as the specific problems themselves are concerned, these relate in a multifaceted way with all of those areas pertaining to cardiovascular research. This includes not only basic research, in very fundamental biochemical, biophysical areas, but the application of research findings to the sick patient.

I think that currently the program is well balanced in the areas of the research that are going on, but I believe that it could be enhanced markedly by the provision of adequate space and the recruitment and training of individuals to carry it on.

Mr. Laird. What should come first?

Dr. Knutti. I think this is perhaps a matter of timing in where you start, sir.

EFFECT OF MATCHING FORMULAS ON RESEARCH FACILITY CONSTRUCTION

Mr. Laird. Do you think there are any medical institutions around the country that are held up on this program because they cannot match, under the medical research facility program?

Dr. Knutti. I am certain there are a number of medical institutions who would have facilities if funds were available on a matching percentage less than 50–50, if I understand you correctly.

Mr. Laird. Do you think they could go 33⅓ percent though?

Dr. Knutti. I would hesitate to try to answer that question, Mr. Laird, without knowing more details.

Mr. LAIRD. Do you think that your Council and the Public Health Service is in a position to make that determination, whether it should be two-thirds and one-third? Do you not think it is just as difficult to make that decision as it is to make a decision on whether it should be zero or 50 percent?

What is the difference in this decisionmaking process that Public Health Service seems to think is simplified by going 33⅓ to 66⅔ percent? Why is it simplified over the program that we have used in the Cancer Institute the last 2 years?

Dr. KNUTTI. Sir, I am not familiar with the program that you have used in the Cancer Institute.

Mr. LAIRD. Maybe you would like to comment on that, Dr. Shannon.

Dr. SHANNON. Yes, Mr. Laird.

Mr. LAIRD. Do you get my point, Doctor?

Dr. SHANNON. Yes; I get your point.

PROBLEMS OF VARIABLE MATCHING PROGRAMS

You have asked two questions: One, are we convinced that we could develop a broad construction program more effectively under a variable matching formula that might provide 2-to-1 instead of 1-to-1 matching; and the second question is, is it any more difficult to run a program with 50–50 matching side by side with a no-matching program than it is to determine the percentage of matching within a single program?

In answer to the first question, whether variable matching or something better than 50–50 matching would be advisable, I think I can state that too frequently the total size of a facility has been determined not by the need but by the money that is available to match the Federal contribution. I have seen too many facilities that are overcrowded when they are put into operation, because they were underbuilt.

If we accept as a serious obligation the need to broaden the base of the medical sciences in this country, and if we accept a continuing obligation for the support of the medical research program to the point that the Federal Government supports something better than 50 percent of the total cost of this research on a continuing basis, then I think it would be in the best interests of the Federal Government to develop its program logically and to expend such additional funds as are needed for capital investments so that the workers who are supported can operate much more effectively. And I do not believe they can, under the present construction programs that are available.

I am convinced that, since the size of the plants that are being developed under our present matching formula are generally determined by the amount of money that can be raised locally, rather than by the need, the relaxation of the matching formula would provide much better planned facilities.

Mr. LAIRD. You are talking about 33⅓?

Dr. SHANNON. Well, any variable matching; 33⅓ would be a good example; yes, sir.

PROBLEMS OF OPERATING SIMULTANEOUS MATCHING AND NONMATCHING PROGRAMS

On the second point—running two programs, one which requires no matching and the other which requires 50–50 matching—I think the problem there is that it is more difficult to run two separate programs than to run a single program.

Maybe we were shortsighted in the way we administered the cancer program during the past 2 years. The deficiency of that approach was that we had the Cancer Council running one program under a "no match" basis, and we had the Research Facility Construction Council running another program on a matching basis.

I think that if these programs were combined and in the hands of a single construction authority to advise the Surgeon General, that they could in fact be run parallel without any great disservice to any one applicant. But I would point out——

Mr. LAIRD. They could be run that way under the present law.

Dr. SHANNON. Yes, sir. I think we are shortsighted in not having them done in that way.

But I would point out that it does not make much sense to run these two programs side by side with a single council when the major difference is between no matching and 50–50 matching. If one were to approach this logically, what one would say, I think, is to have one program in which some proportion of the funds can, in fact, go down as far as no matching, while the remainder can go up as far as is necessary to balance out to some set figure.

CURRENT LEGISLATIVE PROPOSALS

Mr. LAIRD. I testified before the Committee on Interstate and Foreign Commerce on this, and I took exception to the Surgeon General and to the Secretary of Health, Education, and Welfare, in their testimony on this particular point, because I did not believe that their testimony was based upon the experience that we have had in getting facilities constructed in the United States to carry on this kind of research work. I do not believe that, if you follow the recommendations which they made to the Interstate and Foreign Commerce Committee, you will correct the problem that we presently have and that led me to introduce these amendments to the budget for 1961 and 1962.

Did you collaborate in that testimony that was presented by the Secretary and the Surgeon General?

Dr. SHANNON. I suppose some of my people did, but I was away, unfortunately.

Mr. LAIRD. What is your comment on that, Dr. Terry? I know this does not have to do only with the Heart Institute; this has to do with all the institutes.

Dr. TERRY. Yes, sir.

Mr. LAIRD. It seemed to me that in your testimony and the testimony of the Secretary, you failed to touch upon this problem that I believe will continue with us even if this bill is passed in its present form.

Dr. TERRY. I am not even sure what problem you mean. The problem of shortage of facilities?

Mr. **Laird**. The problem of a shortage of facilities, particularly where there could be no matching because of the financial condition of the institution needing the facilities.

You have a lot of these schools that have a tremendous undergraduate population coming up in the next few years, and they are having to put their concentration, as far as the division of the budget is concerned, in many cases at the undergraduate level. With a 33⅓ percent matching requirement, you are not going to help them solve this particular problem on facilities.

You are familiar with the amendments that we have had on the Cancer Institute appropriation the last 2 years?

Dr. **Terry**. Yes; I am familiar with it.

Mr. **Laird**. But you, in your testimony, and also the testimony of the Secretary, did not go along with any nonmatching.

Dr. **Terry**. We did not go along with a no-matching provision.

Mr. **Laird**. Right.

Dr. **Terry**. That is correct, sir.

Frankly, I feel very definitely, Mr. Laird, that where we have money for an intended purpose, that it is not well to have it divided into two pockets, one of which is on one matching basis and another on another nonmatching basis. I think it makes it extremely difficult to administer.

Mr. **Laird**. Well, why do you not administer them through the same council?

Dr. **Terry**. I think it would still be difficult, sir.

Mr. **Laird**. Why is that any more difficult than in deciding whether you are going to give school A 33⅓ percent and school B 66⅔ percent.

Dr. **Terry**. We have not proposed that, sir.

Mr. **Laird**. That is your bill that is before the legislative committee.

Mr. **Kelly**. No.

Dr. **Terry**. No, sir; our bill makes no provision for any matching except a 50–50 basis.

Mr. **Laird**. The position this year that you have taken is to not have a variable matching formula, is that correct?

Dr. **Terry**. That is correct, sir. We have not recommended any change in the matching basis which exists.

Mr. **Laird**. You have also recommended that there be no nonmatching facility construction grants.

Dr. **Terry**. That is right, sir—for local purposes, for an individual institutional purpose, in contrast to a regional or national.

Mr. **Kelly**. And that is enacted in the law. There is no legislative authorization for nonmatching construction grants.

Last year, section 433(a) was amended, effective July 1 of 1962, to repeal the authorization for construction grants.

Mr. **Laird**. Yes, but it was my understanding that the Public Health Service was going to review that and at the time of these hearings was going to make recommendations if they thought it should be changed. And they have made no recommendations, as I understand it, to change this. So the nonmatching program is out the window and you aren't recommending any change in the other program either.

REGIONAL FACILITIES

Mr. **Kelly.** Except for the potential for regional facilities, in the pending legislative proposals; yes, sir.

Mr. **Laird.** Facilities that are regional in nature?

Mr. **Kelly.** Regional or national facilities.

Mr. **Laird.** How big a region does it have to be?

Mr. **Kelly.** It is not defined in the law, sir.

Mr. **Laird.** A couple of counties?

Dr. **Shannon.** No, no.

Dr. **Terry.** I think this is a mistake, Mr. Laird, if one thinks of the regional concept in terms of any specific geographic region. I think you have to adhere to the sort of concept that Dr. Shannon has been trying to portray to you, which is something that goes into other institutions beyond this particular unit, college, school, or university.

Dr. **Shannon.** It would be better if we called it "multi-institutional" rather than regional.

Dr. **Terry.** It would be. I think it would be more correct if I——

Mr. **Laird.** Why do you not amend 433–A to make it "multi-institutional" or whatever you want to call it?

Do you have any comments on that?

Dr. **Terry.** No comments, sir.

Mr. **Laird.** I personally feel you are getting this program pretty fouled up by using this term that you use, "regional in nature" and doing away with all other nonmatching grants. I have not seen you come in here and advocate putting the medical research grants that you are making to investigators on a matching basis. Why have you not done that?

Mr. **Kelly.** There is no question, however, Mr. Laird, that there is a cost participation by the institutions in the research grant program.

Mr. **Laird.** It seems to me that, by putting this term "regional in nature" in your authorization, the Congress has just given you more or less of a blank check anyway, because it is up to you to define what "regional" is.

Mr. **Kelly.** Well, we would have to come before Congress and seek funds for that purpose, and at that point in time, it seems to me, the Congress would——

Mr. **Laird.** What is there in this budget that you are asking to use section 433–A on?

Mr. **Kelly.** I think the only thing that you can put in that category is the primate center, which is a continuation of the program that has already been provided for.

Mr. **Laird.** Well, how much money is involved?

Mr. **Seggel.** $4 million.

Dr. **Shannon.** No, that is wrong. In the 1963 budget there is no money. The only thing in the 1963 budget is operating funds.

Mr. **Kelly.** I see. Yes.

Mr. **Seggel.** That is for the operation of ongoing centers.

Dr. **Shannon.** There is no construction at all for this program in 1963.

DIFFICULTY WITH ADMINISTERING NONMATCHING AND MATCHING PROGRAMS SIMULTANEOUSLY

Mr. KELLY. I would like to say to you, Mr. Laird, that people can differ as to what the matching level should be, and as to whether or not it should be different from that which the administration recommends; but I think it would be fair to say that sound public administration would dictate that, if the Congress is going to authorize or direct the executive branch to carry out programs, that appear on their face to be similar in nature, one of which requires matching and one of which does not require matching, that it should specify to the executive branch either the objectives to be achieved that differentiate the two or the circumstances to be considered which differentiate the two. Then the executive branch can administer the two different programs in a way in which their stewardship will not be criticized for not having carried out the intent of Congress when they cannot fully understand the distinction which Congress is trying to draw.

Mr. LAIRD. You did not have any trouble with those $5 million nonmatching appropriations for each of the last 2 years, did you?

Dr. SHANNON. Well, we did in several instances. And there is probably as much confusion on the institutional end as on the Council end. The confusion came from our requiring—could I leave this off the record?

Mr. LAIRD. Sure.

(Discussion off the record.)

VARIABLE GRANTS UNDER HILL-BURTON PROGRAM

Mr. LAIRD. Let us put this on the record.

The Hill-Burton program has been a variable basis for a long period of time.

Dr. TERRY. That is correct, sir, with a maximum.

Mr. KELLY. The variable in that instance was identified with a legislative measurable and that was the per capita income of the States. Now, we have found no equivalent measurable in connection with colleges and universities, you see.

Mr. LAIRD. Well, I have your book "Grants-in-Aid and Other Financial Assistance Programs 1961 Edition." You will find that it is not just limited to the variable between the States.

I would like to quote from page 25 where it discusses the matching requirements of the Hill-Burton program. This is referring to the matching requirements for individual projects within the State—

> or can vary from one area to another within the allowable range by application of a formula provided in the approved State plan.

There is a variable rate in the States even.

Mr. KELLY. Yes; but this permits the States to use Federal funds to match the local contributions to a hospital at a lesser degree, and thus build more projects than would have been built had they used the maximum Federal contribution in each project. The formula, by law, prescribes an arrangement whereby the maximum Federal matching is established for each State. The State, however, does not have to match each project at that high a level. They can make the Federal funds go further and match more projects.

Mr. LAIRD. I would say that is variable, because you can go anywhere from zero to two-thirds.

Mr. KELLY. You cannot go to zero.

Mr. LAIRD. Why cannot you go down to zero?

Mr. KELLY. With respect to research facilities, there would not be a Federal participation in the project.

Mr. LAIRD. Well, you can go down to 1 percent can you not?

Mr. KELLY. Yes.

Mr. LAIRD. Well, I will correct my remark to say from 1 percent to 66⅔. I would call that a variable program.

Mr. KELLY. Yes, sir.

Mr. LAIRD. And the Hill-Burton program has worked very well.

Mr. KELLY. Yes, sir.

Mr. LAIRD. Now, what is your comment?

Mr. KELLY. If I might turn around the problem you have indicated, however, the local contribution would have to be from 33⅓ percent to 99 percent, using your example.

VARIABLE MATCHING ON NIH RESEARCH FACILITY CONSTRUCTION

In the instance of the research facilities construction, may I say that the same situation prevails, that the local sponsor of the project is required to contribute not less than half of the cost of the facility. In most of the facilities, he is contributing more than half.

As a matter of fact, I think that on the average, they run something like—the Federal contribution is between 25 and 33 percent, is it not?

Dr. SHANNON. Of the total for all institutions.

Mr. KELLY. Of the total cost of the project.

So, again here the sponsor is required to contribute at least 50 percent, but in most instances it is contributing more than 50 percent to the construction of the facility, and this is the exact same situation as prevailed in the Hill-Burton except that the Hill-Burton can go to——

Mr. LAIRD. What is your point? I think you are just proving that this is no problem at all. But I would like to hear what your point is on it.

VARIABLE MATCHING UNDER HILL-BURTON PROGRAM

Mr. KELLY. So far as the Federal administration of the Hill-Burton program is concerned, the degree of variability is established by law, and the Congress has selected the circumstances which create the variability, and the Federal administrators are just carrying this out.

Mr. LAIRD. It would seem to me that the States are not having too much of a problem carrying out this variable matching as far as individual Hill-Burton projects are concerned. Are they better administrators than the Federal Government? Is that why you do not want to get into this area of variable matching?

Mr. KELLY. I would not think that this was true, sir.

PENDING LEGISLATION

Mr. Laird. You are firm in your position, the Department is, that they want this to be straight 50 percent?

Mr. Kelly. It is our position that the number of projects applied for under a 50 percent matching formula exceed the availability of authorized funds.

Mr. Laird. I think you are not going to be able to build some of the most important projects that are needed under that formula. And I am not going to support the bill unless the formula is changed. Of course, I only have one vote and it does not make much difference; but I think that that formula is not going to build the most needed buildings as far as medical research is concerned.

REPORT ON USE OF NONMATCHING CONSTRUCTION FUNDS

I would like a report in the record on the use of the nonmatching program in the amount of $10 million during the last 2 years.

Dr. Shannon. All right.

Mr. Laird. Include in that report how many were unfunded. There must have been some that were unfunded.

Dr. Shannon. Oh, yes.

Mr. Laird. Include those, also.

(The requested information follows:)

Cancer Research Facilities Construction Grants

APPROPRIATION HISTORY

The "National Cancer Institute" appropriation for 1961 included an amount of $5 million for nonmatching cancer research facilities construction grants.

The legislative history indicated that these funds would be granted to institutions having cancer research programs, for the purpose of providing themselves with buildings and equipment needed for the development of their research facilities not otherwise provided for under the health research facilities construction grants program.

PROGRAM ANALYSIS, 1961

In 1961, 33 applications, requesting a total of $28,982,816 were received and reviewed by the National Advisory Cancer Council. Of these applications 17 were recommended for awards for either construction or equipment or both. In accordance with the advisory councils priority ratings, seven of these grants were awarded to six institutions. They are as follows:

University of Wisconsin, McArdle Memorial Laboratory for Cancer Research	$2, 475, 000
University of Wisconsin, Cancer Research Hospital, Madison	488, 000
University of Texas M. D. Anderson Hospital and Tumor Institute, Houston	639, 213
University of Washington, School of Medicine, Seattle	[1] 1, 059, 309
Wistar Institute, Philadelphia	284, 378
Johns Hopkins University School of Hygiene and Public Health, Baltimore	45, 000
Temple University School of Medicine, Philadelphia	49, 100
Total	5, 000, 000

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[1] Because of insufficient funds this award was made in a reduced amount.

PROGRAM PLANS, 1962

In 1962 Congress extended the program for another year by providing $5 million under the appropriation title "Grants for construction of Cancer Research Facilities." In extending this program for another year the Cancer Institute has been able to award funds to institutions already recommended for approval by the National Advisory Cancer Council, but which could not be paid previously because of lack of sufficient funds.

Up to the present time, awards have been made to four institutions as follows:

University of Pennsylvania Veterinary School, Philadelphia	$750, 123
University of North Dakota Medical School, Grand Forks	402, 000
Children's Hospital, Columbus, Ohio	143, 000
State University of Iowa Medical Research Center	206, 000
Total	1, 501, 123

Approval was also recommended by the National Advisory Cancer Council for grants to—

Oklahoma Medical Research Institute, Oklahoma City	$463, 685
California Department of Public Health, Berkeley	1, 180, 000
Total	1, 643, 685

Negotiations regarding these grants have just recently been completed and the awards are being processed.

The award of a grant to the Francis Delafield Hospital, New York City, is still being negotiated. Revised cost estimates are being submitted by the applicant which will serve as a basic for making an award.

Three of the previously recommended applications were brought up for reconsideration at the November meeting of the Council. Two were disapproved and a decision on the third one deferred pending a site visit.

Upon completion of negotiations and final action by the Council on one application an award for construction and fixed equipment will have been made in all recomended applications.

It is expected that sufficient funds will remain to provide awards for movable equipment as recommended by the National Advisory Cancer Council on the basis of $3.50 per net square foot, but not to exceed the requested amounts.

Mr. LAIRD. That is all I have.

Mr. MARSHALL. Dr. Knutti, do you have anything that you would like to add to the testimony before this committee at this time?

Dr. KNUTTI. I think not, sir.

Mr. MARSHALL. If not, we thank all of you for your presentation.

And the committee will stand adjourned until February 19 at 10 o'clock.

Dr. KNUTTI. Thank you very much.

(The following was submitted for the record at the request of the committee:)

DEATHS, DISABILITIES, AND COST OF HEART DISEASE

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, PUBLIC HEALTH SERVICE, NATIONAL HEART INSTITUTE

Statistics of the annual number of deaths and total current number of disabilities caused by each of the major diseases dealt with in the National Heart Institute, and the estimated annual cost to the Nation.

I. Deaths from cardiovascular-renal diseases during 1960 (National Office of Vital Statistics based on 10 percent sample):

Category	*Number*
Arteriosclerotic heart disease (includes coronary disease on "heart attacks")	492,140
Cerebrovascular lesions (includes strokes and other blood diseases in the brain)	192, 720
Hypertension	78, 360
Nonrheumatic chronic endocarditis and other heart muscle degeneration	57, 810
General arteriosclerosis	36, 500
Rheumatic fever and rheumatic heart disease	18, 350
Other cardiovascular diseases	45, 660
Total	921, 540

II. Disabilities from cardiovascular-renal diseases (for year ending June 1958—from U.S. National Health Survey Series B–10, May 1959, and B–13, February 1960):

	Disability category		
	Restricted activity	Sick in bed	Away from work
Number person-days of disability (in millions):			
All cardiovascular-renal diseases	497	173	72
Heart conditions	238	88	
High blood pressure	99	32	
Average number of persons (in thousands):			
All cardiovascular-renal diseases	[1] 1, 362	[1] 474	[2] 288
Heart conditions	652	241	
High blood pressure	271	88	

[1] Person-days/365.

[2] Person-days/250.

NOTE.—These are the figures shown in 1962 hearings. This is not a periodic report, and no later survey has been made.

III. Estimated annual cost to the Nation (from U.S. Income and Output, Department of Commerce, November 1958, and Veterans' Administration):

Compensation and pension payments to veterans disabled by diseases of the circulatory system totaled approximately $464 million in 1960. Lost productivity of those still in the labor force (item II–3, at estimated average earnings of $4,200) for 1958 is estimated at $1,210 million. Figures on expenses of hospitalization and other medical care are not available, nor any figures on which to estimate the productivity loss of persons no longer in the labor force (retired for disability).

(Revised figures on VA compensation and pension payments and on average earnings have been requested and should be available by February 1.)

Highlights of Progress in Heart Research, 1961

Atherosclerosis and Coronary Heart Disease

PRECURSOR CAN SUBSTITUTE FOR CHOLESTEROL IN INFORMATION OF VITAL BILE ACIDS, HORMONES

The drug MER–29 (triparanol, Merrell) inhibits the production of cholesterol, but not of certain vital substances normally made from cholesterol, studies by scientists of the National Heart Institute's Laboratory of Cellular Physiology and of the National Institute of Arthritis and Metabolic Diseases indicate. The blockade of cholesterol synthesis by MER–29 leads to increase serum levels of a precursor, desmosterol, which readily serves in lieu of cholesterol in the production of bile acids, cortisol, and androgens.

In these studies the scientists injected cholesterol labeled with tritium and a desmosterol precursor labeled with carbon 14 into patients receiving MER–29. Subsequent analyses of bile acids and the urinary products of cortisol and the androgenic steroids indicated that, in the synthesis of these compounds, labeled cholesterol and desmosterol had been used to about the same extent as precursors.

Some carbon 14 was also found in cholesterol, indicating that conversion of desmosterol to cholesterol had not been blocked completely by MER–29.

In the body, cholesterol is produced from lanosterol by alteration of its side chain of eight carbon atoms. MER–29 inhibits an enzyme which, at some point in cholesterol production, adds two hydrogen atoms to this side chain. The results of this enzymatic blockade is desmosterol, identical to cholesterol except for the two missing hydrogens. In the synthesis of bile acids, hormones, and steroids from cholesterol, the side chain is removed anyway; so desmosterol is as good a starting material as cholesterol for their synthesis.

Now in clinical use for the treatment of hypercholesterolemia, MER–29 lowers serum cholesterol levels, but the fall in serum cholesterol is usually accompanied by an increase in serum desmosterol, so that total serum sterols may be little affected. Prior to these studies, little was known about desmosterol metabolism in humans, because it is found in significant amounts only in subjects receiving MER–29. These studies confirm the earlier suspicion that the close structural similarity between desmosterol and cholesterol would result in similar biochemical behavior in the body. Only time will tell whether desmosterol may also resemble cholesterol in being atherogenic in man.

Goodman, DeW. S., Avigan, J., and Wilson, H. N.: The metabolism of desmosterol in human subjects during triparanol therapy. Biochem, Pharmacol, 8:87–88, Aug. 1961. (Abstract)

HEART BLOOD SUPPLY, OXYGEN CONSUMPTION REDUCED AFTER HIGH-FAT MEALS

High serum lipid levels following a high-fat meal (postprandial lipemia) are accompanied by a marked reduction in coronary blood flow and in heart oxygen consumption. Heart performance does not appear to be adversely affected. Heparin, which causes rapid clearance of blood lipids, eliminates these effects of postprandial lipemia.

These studies are reported by Drs. T. J. Regan, K. Binak, S. Gordon, V. DiFazio, and H. K. Hellems, of Wayne State University and City of Detroit Receiving Hospital. Their work was supported in part by an NHI grant.

The scientists found that mean coronary blood flow in 7 subjects with postprandial lipemia was 20 percent lower than that in 15 fasting controls. Further, the reduced flow was not compensated by increased oxygen extraction by the heart, so that heart oxygen consumption declined proportionally. The administration of heparin to the lipemic subjects reduced serum "milkiness" by 65 percent within 45 minutes and restored coronary flow and heart oxygen consumption to normal values. These effects of heparin appeared due to its lipid clearing action, since they were not observed in six other lipemic patients in which heparin produced no clearance.

The finding that oxygen extraction by the heart did not increase as coronary blood flow diminished during lipemia suggested that lipemia interferes with blood-to-tissue oxygen transport. Others have reported that lipemia increases the abnormal aggregation, or "clumping" of red blood cells, an effect that would account for the observed diminution both in flow and in oxygen consumption. However, though such an effect might have pertained, it could not be demonstrated in this study. The scientists found no significant differences in blood viscosity between lipemic subjects and the fasted controls.

The lipemia-induced modifications in blood flow and oxygen consumption were not accompanied by any deleterious effects on heart performance in these subjects. Heart rates, heart output, arterial pressure, and stroke volume remained essentially the same during lipemia and after the administration of heparin. Although these observations were made in healthy subjects, the authors suggest that these effects of lipemia also do not contribute significantly to cardiac ischemia in coronary disease. However, they point out, the reduced flow during lipemia, coupled with its reported enhancement of coagulation activity, might be an important factor in the development of coronary blood clots.

Regan, T. J., Binak, K., Gordon, S., DiFazio, V., and Hellems, H. K.: Myocardial blood flow and oxygen consumption during postprandial lipemia and heparin-induced lipolysis. Circulation 23: 55–63, Jan. 1961.

CORONARY PATIENTS MORE SUSCEPTIBLE TO LIPEMIA FOLLOWING FATTY MEALS

Blood fat concentrations, responding to a standard fatty meal, rose higher and lasted longer in patients with coronary heart disease than in age-matched, healthy control subjects. The NHI grant-aided studies failed to show any influence of race or age on fat tolerance.

Drs. I. A. D. Bouchier and B. Bronte-Stewart of the University of Cape Town and Groote Schuur Hospital, Union of South Africa, subjected 146 men to an overnight fast followed by a test breakfast high in butterfat (70 grams). Twenty-nine of these presented electrocardiographic evidence of previous myocardial infarction; 117 healthy men (45 white, 39 Cape Colored, and 33 Bantu) served as normal control subjects. Blood samples were obtained just before the oral fat test and again at 2, 4, 6, and 7½ hours afterward. These samples were centrifuged and the degree of lipemia estimated by optical density measurements of the separated plasma.

The scientists found that patients with ischemic heart disease had a significantly higher degree of lipemia than their age-matched controls, especially at the 6- and 7½-hour periods. The study also revealed a slightly higher degree of fasting lactescence in the patients. No racial or age differences in the fat-tolerance test were demonstrated, report the investigators.

Two series of corollary experiments involving seven patients and seven controls compared the effects of 600 ml. of a fat emulsion (Lipomul I. V., Upjohn Co.) administered intravenously with the same amount of Lipomul given orally. When administered orally, the emulsion—like the high-fat meal—also produced a significantly higher degree of lipemia in the patients than in the normal controls. However, when the emulsion was given intravenously, no such differences were observed.

This interesting finding suggests "* * * that the more intense and long-continued lipaemia in patients with ischaemic heart-disease is due to absorptive mechanisims * * *" rather than to mechanisms for clearing fat from the blood, said the investigators.

Bouchier, I. A. D., and Bronte-Stewart, B.: Alimentary lipaemia and ischaemic heart-disease. The Lancet (7173) 1: 363–366, Feb. 18, 1961.

RATE OF FAT UTILIZATION DEPENDS ON FREE FATTY ACID LEVELS IN BLOOD

Although many investigators noted that epinephrine and norepinephrine increased the rate of fat utilization in skeletal muscles, it was not known whether they acted directly on a self-regulating metabolic system or whether they acted on an outside mechanism which in turn affected the metabolic rate.

Studies in the National Heart Institute Laboratory of Cellular Physiology and Metabolism indicate that the rate of fat utilization is determined simply by the concentration of free fatty acids (unesterified fatty acids) in the blood serum. Free fatty acids are an important mechanism for the transport of lipids from adipose tissue where they are stored as triglycerides, and the concentration of free fatty acids in the blood is determined by the rate of fat mobilization from adipose tissue depots. The hypermetabolism occurring after injection of epinephrine or norepinephrine may be due to a fat-mobilizing action on adipose depots.

In vitro experiments using rat skelital muscle showed that an increase in the concentration of medium free fatty acids resulted in an increase in both the rate of oxidation of fatty acids to carbon dioxide and the rate of deposition of fatty acids in the form of neutral fats (triglycerides). Addition of epinephrine to the isolated system had no effect on either reaction. The addition of glucose had no effect on the rate of oxidation of fatty acids to carbon dioxide. However, the addition of glucose did increase the rate of conversion of fatty acids to triglycerides. This finding indicates that the stores of neutral fat are built up during periods when extra glucose is available, such as immediately after meals.

Since muscle metabolism is a large part of total body metabolism, these findings indicate that the overall metabolic rate probably is greatly influenced by serum free fatty acid levels. Recalling reports of other investigators that serum free fatty acid levels are strikingly elevated in patients with hyperthyroidism, the authors also suggest that the hypermetabolism present during hyperthyroidism may actually be due to the sustained high levels of free fatty acids in the serum which, in turn, could be caused by a more immediate effect of the thyroid hormone.

Eaton, P., and Steinberg, D.: Effects of medium fatty acid concentration, epinephrine, and glucose on palmitate-1-C^{14} oxidation and incorporation into neutral lipids by skelital muscle in vitro. J. Lipid Res. 2: 376–382, Oct. 1961.

ENGULFED PLATELETS SEEN AS SOURCE OF LIPID IN CERTAIN ATHEROSCLEROTIC LESIONS

Experiments reported by Drs. A. B. Chandler and R. A. Hand, NHI grantees at the Medical College of Georgia, support the concept that some atherosclerotic lesions arise from the degeneration and organization of blood clots forming on the walls of blood vessels. Their findings suggest that the lipid-laden foam cells usually found in such lesions may result from the engulfment and digestion of lipid-rich platelets by monocytes also trapped in the clot.

These studies were prompted by the earlier observation that naturally occurring clots in the pulmonary arteries of rabbits underwent conversion into fatty, fibrous atherosclerotic lesions. These lesions contained foam cells derived from entrapped monocytes (a variety of white blood cell) which had engulfed and digested lipid-rich blood platelets, a major constituent of clots.

In the present experiments, the scientists studied clots made in vitro from human plasma and also naturally occurring arterial and venous clots taken at autopsy from human subjects.

The clots made in vitro were incubated in their own plasma for 1–6 days. On the second day of incubation, the scientists observed that many monocytes in these clots had engulfed large numbers of platelets. By the sixth day many of the engulfed platelets had been digested. They were replaced by fat vacuoles in the cytoplasm of the monocytes, which now closely resembled the foam cells often found in atherosclerotic lesions.

The blood clots taken at autopsy were estimated to range from a few hours to several weeks old. Those clots in the early stages of degeneration and organization also contained foam cells; and the scientists observed engulfed platelets in the cytoplasm of entrapped monocytes in 58 of the 134 clots studied. In some clots the scientists also observed monocytes which appeared to be in the process of transition to foam cells. These contained both fat vacuoles and platelets.

These experiments provide additional evidence that some atherosclerotic lesions result from the degeneration and organization of blood clots, the blood platelets of the original clots possibly accounting for the lipid found in such lesions.

Chandler, A. B., and Hand, R. A.: Phagocytized platelets: a source of lipids in human thrombi and antherosclerotic plaques. Science 134: 946–947, Sept. 29, 1961.

ATHEROSCLEROSIS MORE SEVERE IN MEAL-EATING CHICKENS THAN IN NIBBLERS

Experiments with nibbling and meal-eating chickens lead NHI grantees to conclude that consuming food at periodic mealtimes plays a significant role in accentuating the production and in inhibiting the regression of experimental atherosclerosis.

Drs. Clarence Cohn, Ruth Pick, and Louis N. Katz, of Michael Reese Hospital and Medical Center in Chicago, reported their experiments with two groups of chickens. One group, the nibblers, was allowed free access to food 24 hours each day; the other group, the meal eaters, was given food during two 1-hour periods each day.

Both groups were fed a diet containing 20 percent protein, 5 percent cottonseed oil, and 0.5 percent cholesterol. At the end of 5 weeks, the meal eaters had cholesterol levels twice as high and coronary atherosclerosis seven times as severe as did the nibblers, although the meal eaters actually consumed about one-third less food.

In another series of experiments, all chickens were fed an atherogenic diet at periodic mealtimes in order to establish atherosclerosis. Then the chickens were divided into niblers and meal eaters and return to a regular mash diet. Meal eaters exhibited a slower rate of fall of serum cholesterol levels to normal and a marked decrease in the rate of healing of the coronary lesions as compared to the nibblers.

One factor which could help explain these results is that eating large quantities of food at one time necessitates uses of alternate metabolic pathways as well as the primary metabolic pathways involved in the breakdown of foods. One of these alternate pathways which might be called into service also stimulates the generation of TPNH, a factor necessary for the synthesis of lipids and cholesterol.

Another factor may be temporary overloading of the lipoprotein lipase system, which removes cholesterol and other lipids from the blood. This might cause very high serum lipid levels due to inadequate clearance for some time after meals; and these effects, though temporary, might still enhance cholesterol deposition in the arterial wall while they last.

Encouraged by these results and the reports of other investigators, the authors believe that eating habits might well be one factor in the development of atherosclerosis. They cited a recently reported study in which serum lipids were decreased when humans were transferred from meal eating to nibbling. They have also observed one such case and plan to make further studies in humans.

Cohn, C., Pick, R., and Katz, L. N.: Effect of meal eating compared to nibbling upon atherosclerosis in chickens. Circulat. Res. 9: 139–145, Jan. 1961.

SECOND FAT-MOBILIZING HORMONE ISOLATED FROM ANTERIOR PITUITARY

An extract called Fraction H, isolated from the anterior lobe of the hog pituitary gland, has been found to be a potent agent for mobilizing free fatty acids (FFA) from adipose tissue in the rabbit. The active ingredient of this extract has not yet been identified, but has been shown to differ from any other recognized anterior pituitary hormone. The purified extract, though containing no detectable trace of ACTH rivals the potency of ACTH as a lipid mobilizing agent. This, plus similarities in effects produced by the two, leads the authors to speculate that the active ingredient of Fraction H may be related to ACTH in chemical structure.

In these studies, Drs. Mario DiGirolamo, Daniel Rudman, Maria B. Reid, and Floyd Seidman, of Goldwater Memorial Hospital and Columbia University, compared the effects of Fraction H and preparations of the six recognized anterior pituitary hormones on serum FFA levels in the rabbit. They report that only Fraction H and ACTH were highly active in mobilizing FFA.

Equivalent doses of the two produced comparable serum FFA elevations. These reached maximum values within 1 hour after injection and remained elevated for as long as 10 hours, depending upon the size of the dose. When the doses of either hormone were increased, serum FFA levels also increased until a plateau was reached at levels 8–12 times higher than the average pretreatment level. Still larger doses of ACTH or Fraction H could not push FFA levels any higher, but did prolong the period during which these levels remained elevated.

These studies indicate that the anterior lobe of the pituitary contains two potent fat-mobilizing hormones: ACTH and the active ingredient of Fraction H. They also suggest that the two may be similar in chemical structure. It has also been shown that the hog pituitary contains 2–4 times as much Fraction H as ACTH. However, it remains to be determined whether Fraction H plays any physiological role in fat mobilization, and if so, how large that role might be.

Di Girolamo, M., Rudman, D., Reid, M.B., and Seidman, F.: Effect of pituitary hormones upon serum free fatty acid concentratiton of the rabbit. Endocrinology 68:457–465, Mar. 1961.

DIETARY PECTIN CAUSES SLIGHT BUT SIGNIFICANT REDUCTION OF CHOLESTEROL LEVELS

Although the kind and amounts of fats eaten appear to be the most important dietary determinant of serum cholesterol levels, a dietary carbohydrate, pectin, has also been found to produce a slight but consistent reduction of serum cholesterol in man, report Drs. Ancel Keys, Francisco Grande, and J. T. Anderson of the University of Minnesota, Minn., and the Hastings State Hospital, Hastings, Minn. Their study was aided by a research grant from the National Heart Institute.

Found in many fruits and vegetables, pectin is the complex carbohydrate that puts the "jel" in fruit jellies. That either pectin or plant cellulose (fiber) might lower serum cholesterol was suggested by the Minnesota scientists' previous work. Clinical experiments involving diets comparable in calories, proteins and fats but differing in that an abundance of fruits and vegetables in one diet replaced simpler carbohydrates in the other, had shown that the diet high in fruits and vegetables produced lower serum cholesterol levels.

In the currently reported studies, they compared the cholesterolemic effects of pectin- or cellulose-supplemented natural diets with those of nonsupplemented diets in a group of 49 physically healthy, middle-aged, male mental patients. Pure citrus pectin or cellulose, incorporated into special biscuits, was given at the level of 15 grams daily for a period of 3 weeks.

Biscuits similar in appearance and caloric content but lacking either supplement, were given during alternate 3-week periods.

Comparison of serum total cholesterols at the end of each dietary period showed no effect of cellulose supplements but did reveal a statistically significant effect of adding pectin to the diet: serum cholesterol levels fell an average of 5 percent below the levels on the same diet without pectin.

From available but incomplete information on the cellulose and pectin contents of natural foods, Dr. Keys and coworkers suggest that the amounts used in this study "* * * correspond to the upper levels of these substances provided in natural human diets." They add, "The largest usual source of pectin in human diets is probably in apples; but 15 grams daily, as used here, would be obtained from this source only by a most enthusiastic apple eater."

Keys, A., Grande, F., and Anderson, J. T.: Fiber and pectin in the diet and serum cholesterol concentration in man. Proc. Soc. Exp. Biol. Med. 106: 555–558, Mar. 1961.

BLOOD CHOLESTEROL LEVELS SHOW STRIKING PATTERN OF SEASONAL VARIATION

A striking pattern of seasonal variation in the serum cholesterol levels of healthy young males has been observed by NHI grantees, Drs. Caroline B. Thomas of Johns Hopkins, and H. W. D. Holljes and F. F. Eisenberg of the University of Maryland.

Their analysis of a series of 14 serum cholesterol determinations, made over the course of a year in each of 24 healthy male subjects, revealed that serum cholesterol levels rose sharply in November, remained on a high plateau through January, then declined gradually, reaching lowest values for the year during late spring and summer.

At the beginning of the study, the subjects (volunteers from the Maryland State Penitentiary) were divided into three groups: those with high, those with intermediate, and those with low serum cholesterol levels. The same seasonal pattern was observed in all three groups.

The scientists could find no correlations between this seasonal pattern and such factors as the subjects' degree of physical activity (work or exercise), smoking habits, or weight changes. Such dietary data as was available indicated no seasonal variations in fat intake large enough to account for the observed pattern, nor did psychic stress appear to be a factor. Seasonal variations in the activity of certain endocrine glands, which might bear importantly on serum cholesterol patterns, have been reported by others: however, no attempt was made to evaluate such factors in this study.

Whatever the course of this seasonal pattern, the authors conclude, it should always be considered when evaluating the significance of serum cholesterol levels in research or clinical situations.

Thomas, C. B., Holljes, H. W. D., and Eisenberg, F. F.: Observations on seasonal variations in total serum cholesterol level among healthy young prisoners. Ann. Intern, Med. 54: 413–430, Mar. 1961.

HEART FIBRILLATION DURING BLOOD DEPRIVATION NOT DUE CHIEFLY TO OXYGEN LACK

NHI grantees have compared the effects of an inadequate coronary blood supply (cardiac ischemia) and of an inadequate oxygen supply (hypoxia) on the electrical conduction system of the heart. This system, which originates and transmits the electrical impulses causing the heart muscle to contract, was far more sensitive to blood deprivation than to inadequate oxygen alone. The studies suggest that the disruption of normal cardiac electrical activity produced by blood deprivation is due less to inadequate oxygen than to such factors as local changes in blood acidity or alkalinity, waste product retention, or changes in electrolyte concentrations.

The studies were conducted by Drs. A. A. Bagdonas, J. H. Stuckey, J. Piera, H. S. Amer, and B. F. Hoffman, of the State University of New York, Downstate Medical Center, Brooklyn.

The electrical impulses causing heart muscle contraction originate in the sinoatrial node, the heart's pacemaker, located in the upper right quadrant of the right atrium. Traveling through the atrial muscle fibers, these impluses first activate the atrio-ventricular node, located in the lower left quadrant of the right atrium. The impulses then enter the bundle of His, a sheaf of specialized conduction tissue running along the muscle wall that divides the left and right sides of the heart. This bundle divides into left and right branches, which further divide into the Purkinje network, whose fibers fan out over the inner surfaces of the left and right ventricles.

The effects of blood deprivation and inadequate oxygen on this system were studied in dogs. Seven electrodes monitored electrical activity at various points on the heart surface, in the bundle of His, and in the bundle branches or Purkinje fibers.

In these studies, an inadequate blood supply invariably disrupted the contraction rhythm in the ventricles (fibrillation) by interfering with their electrical activity; inadequate oxygen never did. The atrio-ventricular node, the sinoatrial node, and the atria (in that order) were the most sensitive both to inadequate blood and to inadequate oxygen. Except for the atrio-ventricular node, the electrical conduction system appeared more resistant to an inadequate blood supply than the heart muscle fibers, and was little affected, even by 120 minutes of severe oxygen deprivation.

These striking differences between the effects of blood deprivation and of oxgen deprivation on the conduction system led the authors to conclude that oxygen deficiency during blood deprivation is far less important than other metabolic factors.

Bagdonas, A. A. Stuckey, J. H. Piera, J., Amer, N. S., and Hoffman, B. F.: Effects of ischemia and hypoxia on the specialized conducting system of the canine heart. Amer. Heart. J. 61: 206–218, Feb. 1961.

RISK FACTORS IN DEVELOPMENT OF CORONARY DISEASE REPORTED FROM COMMUNITY STUDY

The risk of developing coronary heart disease for men 40 to 60 years of age is almost three times as great for those who have either a high blood cholesterol level, high blood pressure, or an enlarged left ventricle, as it is for those who are normal in these respects.

This finding was one of the results reported from 6 years of followup in the long term epidemiological study being conducted by the Heart Institute at Framingham, Mass. In this study, a cross section of the adult residents of the community is being observed over a long period of time to find out how many of them developed heart disease, when it develops, and what factors are associated with it.

The investigators, Drs. W. B, Kannel, T. R. Dawber, A. Kagan, N. Revotskie, and J. Stokes III, reported also that combinations of any two or all three of the cited abnormalities further increased the risk of coronary disease. It was found that for men 40 to 60 years of age whose cholesterol level, blood pressure, and left ventricle size were normal, the 6-year incidence of coronary heart disease was 36 per thousand. For men in this same age group who had all three abnormalities, however, the incidence rose to approximately 500 per thousand.

Considerable difference between the sexes on factors associated with development of coronary disease was revealed in the study. A high blood cholesterol level (245 milligrams percent or above) was associated with a more than threefold increase in risk among men 40 to 60 years old, but contributed only slightly to an increased risk in women the same age. On the other hand, high blood pressure was associated with a twofold risk increase for men as contrasted with a sixfold increase in risk for women.

Other findings further pointed up the significance of the sex differential as a factor. Of the 5,127 persons in the study who did not have coronary heart disease when first examined, 186 developed the disease during the 6-year period of observation. Thirty-four were in the age range from 30 to 45, with an incidence ratio of 13 men to 1 woman. One hundred and fifty-two were in the age range from 45 to 60, with the ratio at these older ages decreasing to approximately 2 men to 1 woman.

This type of coronary disease was found to be more severe in the men than the women. Angina pectoris alone occurred in 70 percent of the women but in only 30 percent of the men. Coronary heart disease in men was chiefly manifested as myocardial infarction or sudden death. Sudden death was four times as common in men as in women.

The investigators also reported that 39 (approximately 45 percent) of the 88 men who developed myocardial infarction during the 6 years of observation were not hospitalized. Sudden death occurred in one-half of those not hospitalized and another 23 percent of them experienced "silent" infarctions which went unrecognized until revealed by routine electrocardiograms at subsequent regular examinations.

Kannel, W. B., Dawber, T. R. Kagan, A., Revotskie, N. and Stokes, J., III: Factors of risk in the development of coronary heart disease—6-year followup experience; the Framingham study, Ann. Intern. Med. 55: 33–50, July 1961.

Blood Pressure

NEW MAO INHIBITOR EFFECTIVE AGAINST HIGH BLOOD PRESSURE IN NHI CLINICAL TRIALS

A new monoamine oxidase inhibitor, MO–911 (Abbott), has performed effectively as a therapeutic agent for hypertension in clinical trials conducted by National Heart Institute scientists. The new drug has been found highly effective in lowering standing blood pressure in nine hypertensive patients. The compound is a potent inhibitor of monoamine oxidase (MAO), but appears to be free from toxic effects that had blighted the promise shown by several MAO inhibitors tested previously. The clinical trials were conducted by Drs. Albert Sjoerdsma and David Horwitz, of the NHI Experimental Therapeutics Branch.

Monoamine oxidase is an enzyme which inactivates norepinephrine, tryptaine, and certain other amines which appear to be intimately involved in bodily mechanisms for the control of blood pressure. A number of compounds which block the action of this enzyme had been found to be powerful agents for lowering blood pressure; however, they also produced severe side effects that prohibited their use in the treatment of hypertension. MO–911 is similar in its effects on monoamine oxidase and on blood pressure, but differs markedly in chemical structure from these earlier MAO inhibitors (all of which were hydrazine derivatives) and also in its apparent freedom from adverse side effects. Both the differences and the similarities are important. They indicate that MAO inhibition is indeed the key to the hypotensive action of all of these compounds, but that inhibition of this enzyme per se probably is not responsible for the toxicity of any of them.

The present study indicates that MO–911 is a potent hypotensive agent very well suited to the treatment of the ambulatory hypertensive. Its hypotensive effects develop gradually, after which a single daily dose of 75–125 mg. of the drug is usually sufficient to maintain standing blood pressure at satisfactory levels. However, though MO–911 appears to hold great promise as a therapeutic agent, extended clinical trials will be necessary to determine whether the new drug retains its freedom from toxic effects when used over long periods of time.

The discovery of MO–911 was announced in 1960 by J. D. Taylor and coworkers of Abbott Laboratories, North Chicago, Ill., who also supplied the MO–911 used in these studies.

Horwitz, D. and Sjoerdsma, A.: A nonhydrazine monoamine oxidase inhibitor with antihypertensive properties. Proc. Soc. Exp. Biol. Med. 106: 118–120, Jan. 1961.

RESPONSE OF MATERNAL, FETAL CIRCULATIONS TO VASOACTIVE DRUGS EVALUATED

Drug-induced changes in pressure and flow in the maternal circulation of sheep have no significant effects on the fetal circulation and vice versa, according to studies reported by Drs. F. H. Adams, Nicholas Assali, Marjorie Cushman, and A. Westersten, National Heart Institute grantees at the University of California Medical Center.

These studies were performed on ewes between their 110th and 130th days of pregnancy (normal gestation period: 144–151 days). Fetal circulatory measurements were made while the fetus was still in the uterus. Great care was taken to avoid interfering with normal fetal circulation and to maintain conditions closely approximating normal in utero conditions.

The scientists made simultaneous measurements of pressure and flow in both the maternal and fetal circulations, following injections into the mother or into the fetus of epinephrine, norepinephrine, and angiotensin—all potent vasoconstrictors.

When injected into the mother, epinephrine or norepinephrine cause a sharp rise in uterine artery pressure, afall in uterine flow, and irregularities in the maternal heart rate and rhythm. Angiotensin increased both pressure and flow in the uterine artery. However, none of these produced any significant effect on pressure or flow in the fetal circulation or on fetal heart rate.

When injected into the fetal circulation via an unbilical vein, epinephrine or norepinephrine could increase both pressure and flow in the umbilical arteries, but only in doses equivalent to five times the adult dose. Angiotensin had no effect even in doses 10–12 times the equivalent adult dose. None of these injections into the fetal circulation produced any effect on the maternal circulation.

These studies indicate that these vasoactive drugs do not cross the placental barrier in physiologically significant amounts. Further, the fetus appears to be insulated to some degree against pressure and flow changes induced in the maternal circulation by such drugs.

Adams, F. H., Assali, N., Cushman, M., and Westersten, A.: Interrelationships of maternal and fetal circulations. I. Flow-pressure responses to vasoactive drugs in sheep. Pediatrics 27: 627–635, Apr. 1961.

BOTH ACTIVE, PASSIVE UPTAKE OF NOREPINEPHRINE FOUND IN BRAIN, HEART, AND SPLEEN

National Heart Institute studies indicate that the uptake of norepinephrine (NE) by brain, heart, and spleen proceeds both by passive diffusion and by a low-capacity concentrating mechanism. When the tissue medium contains little NE, its uptake by these tissues is chiefly by the concentrating mechanism, which probably involves a carrier enzyme and appears to use energy generated by cell metabolism to move NE into the tissues against an opposing concentration gradient. When the medium contains higher concentrations, however, the mechanism becomes saturated, and uptake above this saturation value proceeds by passive diffusion.

These studies were conducted by Drs. H. J. Dengler, H. E. Spiegel, and E. O. Titus, of the NHI Laboratory of Chemical Pharmacology.

The scientists measured the uptake of norepinephrine labeled with tritium in tissue slices from various parts of the brain and from heart, spleen, liver, adrenal cortex, and muscle. All of these tissues have adrenergic nerves (for which NE is the neurohormone), and brain, heart, spleen, and adrenal cortex contain large quantities of stored norepinephrine.

The experiments demonstrated a norepinephrine concentrating mechanism in brain, heart, and spleen tissue. When the incubation medium contained low NE concentrations (5–25 micrograms/ml.), tissue concentrations rose as high as four times that of the medium. When the medium contained higher concentrations, the NE "pump" became saturated. Uptake above this saturation value was by passive diffusion, the tissue NE concentrations increasingly reflecting those of the medium. No concentrating mechanism was evident in tissue from liver, muscle, or, surprisingly, from the adrenal cortex, a major source of circulating NE.

The concentrating mechanism was blocked when reserpine or metabolic inhibitors such as ouabain were added to the medium. This suggested that the mechanism involved active NE transport, using energy derived from cell metabolism to overcome an unfavorable concentration gradient. However, the present studies did not rule out the possibility that the mechanism might involve chemical binding or adsorption of NE by tissue components.

The scientists noted that the drugs that inhibited the concentrating mechanism also sensitize adrenergic organs to administered NE. Thus the mechanism might play an important role in ending the biological action of NE on these organs by taking it up for delivery to an intracellular storage site. This cellular redistribution would neutralize the action of NE as effectively as would its destruction by monoamine oxidase or other enzymes.

Dengler, H. J., Spiegel, H. E., and Titus, E. O.; Uptake of tritium-labeled norepinephrine in brain and other tissues of cat in vitro. Science 133: 1072–1073, Apr. 7, 1961.

HEART RECHARGES CERTAIN NERVE ENDINGS WITH BLOOD CATECHOL AMINES

Heart Institute scientists have found that continued stimulation of cardiac sympathetic nerves partially depletes the heart of the catechol amines—epinephrine and norepinephrine—stored in the heart muscle. They have also found that the heart can replenish its supply of these amines by extracting them from the blood. The studies, carried out by Drs. J. H. Siegel, J. P. Gilmore, and S. J. Sarnoff of NHI's Laboratory of Cardiovascular Physiology, indicate that this might well be an important mechanism by which the heart continuously recharges its sympathetic nerve endings.

Epinephrine and norepinephrine, which increase heart output by increasing heart rate and by increasing the vigor of cardiac contraction, are released from the adrenal glands in response to stress, exercise, and other stimuli, and reach the heart via its blood supply. They are also liberated from stores within the heart muscle itself when the heart's sympathetic nerves are stimulated. In either case, their effects on heart performance are the same.

The NHI studies showed that the extraction of catechol amines by the heart was primarily dependent upon the quantities presented to it in the coronary blood supply and upon the amounts already stored in the heart. Extraction apparently does not depend upon the ability of the heart to use the amines, since it continued after the main sympathetic nerve trunks had been cut, or after drugs that block the action of these amines had been administered. However, undegenerated nerve endings do appear essential. Other NHI studies have shown that a completely denervated heart cannot store catechol amines, even though its response to administered amines is actually intensified. It appears likely that the nerve endings are the chief amine storage sites, and they may also play some important role in the absorptive mechanism.

The liberation of stored catechol amines by smypathetic stimulation was found to be proportional to the intensity of the stimulus. The hemodynamic response of the heart, in turn, was directly proportional to the quantities of amines released.

Siegel, J. H., Gilmore, J. P., and Sarnoff, S. J.: Myocardial extraction and production of catechol amines. Circulat. Res. (in press).

SYMPATHETIC NERVES MEDIATE SOME HORMONAL EFFECTS IN HYPERTHYROIDISM

Hyperthyroidism is the result of excessive secretion of thyroxine and/or other thyroid hormones. Among the clinical signs of this disorder are stepped-up metabolism, increased heart rate and blood pressure, weight loss, nervousness and tremors. NHI studies indicate that certain of these hormonal effects are mediated, at least in part, by the sympathetic nervous system.

Drs. T. E. Gaffney and Eugene Braunwald, of the NHI Cardiology Branch, studied the effects of guanethidine (CIBA) on heart rate, blood pressure, weight loss, basal metabolic rate, and serum cholesterol levels in four healthy volunteers made hyperthyroid with triiodothyronine (T3), a thyroid hormone.

In addition to its expected reduction of blood pressure, guanethidine abolished the increases in heart rate and reduced the elevated metabolic rates, tremors, and restlessness produced in these subjects by T3.

The rate of weight loss and the lowered serum cholesterol produced by T3 were not noticeably affected by guanethidine.

Guanethidine, widely used against hypertension, selectively blocks nerve impulse transmission in the sympathetic (excitor) division of the autonomic nervous system, whose two opposing divisions regulate body functions not under conscious control.

The drug appears to be highly specific in its site of action. It depletes the sympathetic nerve terminals of norepinephrine, a neurohormone that is necessary to the transmission of nerve impulses between these nerve endings and their effector organs. Thus, this action blocks sympathetic transmission almost as effectively as if the nerves had been cut.

The finding that guanethidine also abolished or reduced certain of the manifestations of hyperthyroidism suggested that these hormonal effects, especially those on heart rate, were mediated (at least in part) by the sympathetic nervous system.

The reduction of basal metabolic rate caused by guanethidine is puzzling, especially since the drug did not affect serum cholesterol or weight loss in the subjects. It is possible that this effect was secondary to the drug's reduction of heart rate, blood pressure, and restlessness.

These studies suggest that guanethidine might be valuable in the treatment of hyperthyroidism, though no substitute for specific antithyroid drugs. It might also be used advantageously in connection with thyroid hormone therapy sometimes resorted to for reducing serum cholesterol levels in hypercholesterolemia. The drug would not impede the hormone's action on serum cholesterol, but would eliminate or reduce some of its undesirable side effects.

Gaffney, T. E. and Braunwald, E.: An analysis of the hemodynamic effects of guanethidine. Clin. Res. 9: 139, Apr. 1961. (Abstract)

PLASMA CARDIOGLOBULINS ACT TO MAINTAIN NORMAL HEART MUSCLE CONTRACTILITY

Plasma assays of patients with various types of cardiovascular disease provide evidence that the cardioglobulins, a group of protein substances found in the blood plasma of man and other mammals, are essential for maintaining normal contractility of heart muscle, report Drs. Stephen Hajdu and Edward Leonard of the National Heart Institutes Laboratory of Kidney and Electrolyte Metabolism.

The cardioglobulin system was discovered several years ago when the NHI scientists found that the contractile response of artifically stimulated frog heart could be increased by adding small amounts of mammalian plasma. This action is similar to (but chemically unlike) that of digitalis, a plant extract used in the treatment of heart failure. Subsequent studies showed that: 1) the cardioglobulin system is made up of three proteins, cardioglobulins A, B, C; 2) all three substances are needed to cause activity; and 3) higher than normal activity in patients with severe hypertension is due to increased amounts of cardioglobulin C.

In the currently reported studies, Drs. Leonard and Hajdu used bioassay techniques (based on the action of the cardioglobulin system on the isolated frog heart) to measure cardioglobulin C concentrations in patients suffering from hypertension, aortic stenosis, aortic insufficiency, or congestive heart failure.

They found elevated cardioglobulin C levels in diseases characterized by increased left ventricular blood pressure, i.e., in hypertension and aortic stenosis. Essentially normal cardioglobulin levels were found in normal volunteers and in patients with aortic insufficiency, a disease associated with increased stroke volume but not increased left ventricular pressure. Thus, increased cardioglobulin activity appeared to be an adaptive response which, by increasing heart muscle contractility, enabled the heart to maintain its normal output under conditions of increased left ventricular pressure.

The scientists reasoned further that, if the cardioglobulin system were necessary for normal heart muscle contractility, cardioglobulin deficiency could perhaps lead to decreased contractility and congestive heart failure. They tested this postulate by measuring cardioglobulin levels in patients with congestive heart failure secondary to know valvular disease and in other patients whose congestive heart failure was of unknown cause but believed due to a primary defect in heart muscle contractility. They found that more than half of the patients in the latter group had extremely low cardioglobulin concentrations, whereas values for all other congestive heart failure patients fell within the normal range. The scientists conclude that these findings "* * * are consistent with the idea that among patients with idiopathic cardiac muscle disease there are some who have a primary deficiency of cardioglobulin which perhaps leads to the development of cardiac failure.

Future studies of the cardioglobulin system will be extended to include other types of cardiovascular disease and to determine the effects of therapeutic drugs and remedial surgery on cardioglobulin activity.

Hajdu, S. and Leonard, E.: Cardioglobulin; assay methods. Circulat. Res. 9:881–890, July 1961.

Leonard, E. and Hajdu, S.: Cardioglobulin; clinical correlations. Circulat. Res. 9:891–896 July 1961.

SURGERY

HAZARD OF HEART OPERATION POSTPONED IN SOME INFANTS BY PALLIATIVE SURGERY

Present surgical techniques provide a relatively safe method of correcting ventricular septal defects in children at least 3 or 4 years old, but they are still hazardous when used in infants or very young children. However, many infants whose defects are not treated immediately do not survive because of excessive pulmonary blood flow which causes congestive heart failure. The heart failure is often complicated by repeated and severe pulmonary infections.

National Heart Institute surgeons, Drs. Andrew G. Morrow and Nina Braunwald, report their treatment of 13 selected infants with ventricular septal defects using a modification of the operative procedure described by Damman and

Muller. This procedure involves constricting the pulmonary arteries to prevent excessive pulmonary blood flow. Twelve children survived the operation, and after 1 to 4 years, all show striking improvement in growth, weight gain, and exercise tolerance. None has suffered pneumonia or heart failure since the operation. However, this procedure is not a cure, and correction of the defect is still required.

The patients, aged from 3 to 22 months, were selected on the basis of diagnosis, age, general physical condition, and response to intensive pediatric management during prolonged hospitalization. Preoperative cardiac catheterization was used to establish accurately the diagnosis of ventricular septal defect.

Reduction in pulmonary blood flow, the immediate objective of the operation, averaged approximately 33 percent in these patients. Reduction was estimated by determining the mean pulmonary arterial pressure, with pressure measurements made while heart action is vigorous. The surgeons found that under optimal conditions pulmonary arteries should be constricted enough to reduce the mean pulmonary arterial pressure 30 to 40 percent.

This constriction may be helpful in preventing or improving enlargement of the pulmonary arterioles, considered to be related to increased pulmonary blood flow and high pulmonary arterial pressure.

Morrow, A. G. and Braunwald, N. S.: The surgical treatment of ventricular septal defect in infancy; the technic and results of pulmonary artery constriction. Circulation 24: 34–40, July 1961.

FIBRINOLYTIC THERAPY SEEN AS VALUABLE ADJUNCT TO SURGERY IN THROMBOEMBOLIC DISEASES

Surgical removal of clots blocking large vessels is attended by the risk that the clot might re-form or that fresh clots might develop in collateral vessels—a risk not completely eliminated by anticoagulants. Dr. William Anlyan and coworkers, NHI grantees at Duke University, report that fibrinolysin is highly effective against such clots if treatment is begun promptly.

Most of the 37 patients in this series had postsurgical clots or emboli blocking blood vessels of the extremities. Fibrinolysin (Thrombolysin, Merck, Sharp & Dohme) was administered into the affected part via a distal vein whenever possible. Doses were adjusted to reduce prothrombin time, as an index of clotting ability, to 35–40 percent of normal and to keep it so for about 48 hours.

Evaluation by arteriography or return of pulses (16 patients) or on the basis of general clinical improvement indicated that most patients were helped by the therapy. In some, the grantees report, it probably saved limbs or substantial parts of limbs from amputation. Therapy was generally ineffective against clots or emboli more than 48 hours old. No adverse effects of the drug were noted. The scientists conclude that fibrinolytic therapy is a valuable adjunct to surgery in thromboembolic diseases.

Anlyan, W. G., Silver, D., Deaton, H. L. Fort, L., III, and Webster, J. L.: Fibrinolytic agents in surgical practice; their role as an adjunct to surgical treatment of thromboembolic disease in 37 patients. JAMA 175: 290–292, Jan. 28, 1961.

BLOOD VESSEL X-RAYS SAFER, SURER WITH DEXTRAN PREMEDICATION

NHI grantees report that infusions of low-molecular-weight dextran allow higher safe dosage levels of injected radiopaque contrast agents in man and animals.

The diatrizoate X-ray contrast compounds, when injected rapidly and in large amounts, cause diffuse clumping of red blood cells and other serious complications culminating in death. Previous studies by Dr. Eugene F. Bernstein and coworkers at the University of Minnesota Medical School had shown that, in dogs, the 50- and 100-percent lethal doses of one of these compounds, Hypaque-90, can be doubled by pretreatment with a low-molecular-weight dextran solution, 10 cc./kg. administered intravenously. The currently reported experiments compared the protective effects of LMW dextran with those of equal amounts of other commonly used parenteral agents—saline, dextrose, dog plasma, human albumin, or commercial dextran—in dogs subsequently challenged with a uniformly fatal dose of Hypaque-90 (5 cc./kg.). These effects, calculated from whole blood and plasma viscosity and blood hematocrit, were expressed as "apparent RBC viscosity" (the component of blood viscosity due to red blood cells).

The scientists found that apparent RBC viscosity was essentially normal in LMW dextran-pretreated dogs, considerably higher in the other experimental dogs (60-percent higher in the saline group), and more than doubled in animals without premedication. These RBC viscosity studies correlated with direct observations of the microcirculation in delicate eye membranes: red blood cell aggregates were absent or markedly decreased in the dextran-pretreated dogs in contrast to the other groups. And, while each premedication solution caused some decrease in mortality, none approached the activity of LMW dextran in this respect.

The Minnesota scientists also report their preliminary clinical observations of 21 dextran-pretreated patients undergoing diagnostic aortography with high doses of Hypaque-90 (1.06–1.78 cc./kg.). No mortality or serious complications occurred in the dextran-protected patients, although slight, transient electrocardiographic changes were noted in some of them. "It is our impression in this small series of cases that the quality of contrast seen in the abdominal aorta is superior to that noted in our previous experience with over 200 cases in which no premedication was given and a dose of 0.7 to 1.3 cc. of Hypaque-90/kg. was administered," report the scientists.

These findings are reported by Drs. Bernstein, R. L. Evans, J. A. Blum, and Mr. R. F. Avant, whose studies were supported in part by an NHI research grant.

Dextran is a polysaccharide produced from molasses, dairy products, and vegetables by the action of certain bacteria. In ordinary medical usage as a blood plasma expander, it has a molecular weight of approximately 75,000. The specially processed dextran used in these studies (Rheomacrodex, Pharmacia, Inc.) has a molecular weight of about 40,000.

Bernstein, E. F., Evans, R. L., Blum, J. A., and Avant, R. F.: Further experimental and early clinical observations concerning the protective action of low molecular weight dextran upon intravenous hypaque toxicity. Radiology 76: 260–261, Feb. 1961.

PRECORDIAL DILUTION METHOD MEASURES LEFT VENTRICULAR BLOOD VOLUME

National Heart Institute investigators have developed a simple technique which can be routinely applied during left heart catheterization to measure left ventricular blood volume.

This technique, known as the precordial dilution technique, can be used to detect ventricular failure and is valuable for general studies of left ventricular function. It is also useful in detecting two forms of acquired heart disease: mitral valve regurgitation and aortic valve regurgitation.

The investigators first catheterize the left heart by the transseptal technique. They pass a special hollow needle in a catheter through a vein in the leg on to the right atrium. The needle is used to puncture the septum which separates the right and left atria. A smaller catheter is passed through the needle into the left atrium, then through the mitral valve into the left ventricle.

They next inject a radioactive indicator (Diodrast with radioactive iodine) rapidly into the apex of the left ventricle. The indicator is introduced through multiple openings in the catheter to insure complete mixing with ventricular blood. A scintillation detector placed on the chest wall over the left ventricle (the region known as the precordium) measures the concentration of indicator. When these concentrations are plotted on a graph, the scientists use the resulting dilution curve to estimate what fraction of the total blood volume present in the left ventricle at the end of diastole (dilation) is ejected during each heart beat.

Other methods using the indicator-dilution principle have been employed to measure heart function. However, nonisotopic indicators must be measured in a sample withdrawn through a second ventricular catheter. The use of two catheters is technically much more complex than the use of one, and the results are often inaccurate due to inadequate mixing of the indicator and ventricular blood.

In previous studies using radioisotopic indicators, the indicators were introduced before the blood reached the ventricle. Therefore the resulting dilution curve indicated not the rate at which the indicator left the ventricle but the difference between the rate of entry and the rate of exit.

The accuracy of the technique was demonstrated first in a circulatory model and then in dogs. When the technique was used on 40 patients, 20 with normal hearts and 20 with heart failure or valvular regurgitation, it proved to be sensitive to changes in ventricular function.

Folse, R., Braunwald, E., and Aygen, M. M.: Clinical technic for determining the fraction of left ventricular end-diastolic volume ejected per beat. Circulation 24: pt. 2,934, Oct. 1961. (Abstract.)

INFANT WITH FUSED VALVE SAVED BY RIGHT HEART BYPASS OPERATION

NHI grantees at the University of Alabama Medical Center have successfully bypassed a congenitally closed tricuspid valve by shunting blood from the superior vena cava directly into the right pulmonary artery. This procedure saved the life of a 14-week-old infant with tricuspid atresia blocking normal blood flow between the right atrium and right ventricle which pumps blood to the lungs.

Drs. W. Sterling Edwards and L. M. Bargeron, Jr., report that, before the operation, the only blood reaching the infant's lungs was that which bypassed the obstructed tricuspid valve through atrial and ventricular septal defects. But though these other malformations compensated the tricuspid atresia to some extent, blood flow to the lungs was further compromised by a constricted pulmonary valve.

At operation the surgeons cut the right pulmonary artery just above the heart and closed off the stump. The free end of this artery was then inserted through a slit made in the superior vena cava and sutured into place. The vena cava was tied off just beyond this point so that all of the blood from the superior vena cava was diverted directly into the pulmonary artery.

Following surgery, the child's color returned, the heart and liver decreased in size, and arterial oxygen saturation increased from a pre-operative level of 65 percent to between 80 and 85 percent. The surgeons report that this patient is the first with tricuspid atresia, and the youngest ever, to benefit from right heart bypass.

The favorable results in this infant demonstrate the feasibility of small anastomoses in the low-pressure venous system. "If subsequent experience with the vena cava-pulmonary artery shunt is as favorable as in this case, this would seem to be the operation of choice for tricuspid atresia," they conclude.

Edwards, W. S. and Bargeron, L. M., Jr.: Superior vena cava to pulmonary artery shunt for tricuspid atresia in an infant. Surgery 49: 205–208, Feb. 1961.

CERTAIN STROKE PATIENTS BENEFITED BY ARTERIAL RECONSTRUCTION SURGERY

National Heart Institute grantees report their experiences with 895 patients and conclude that many patients suffering from cerebral artery insufficiency cause by extracranial arterial occlusion can benefit from the arterial reconstruction operation.

Often the lesions induced by arteriosclerosis and responsible for arterial insufficiency in vessels leading to the brain and to other parts of the body are well localized. Cerebral arterial lesions are often localized outside the brain in the neck or chest. Arteriographic studies can be used to determine which patients can most benefit from surgical treatment.

Arteriographic examination of 895 patients—861 with various neurologic symptoms of cerebral artery insufficiency, 17 with ear noises or systolic murmurs in the neck, and 17 with insufficient blood flow to the arm—revealed extracranial arterial occlusion in 361 patients. Of these, 326 patients were treated. Normal blood flow was restored either by removing the occlusion and repairing the artery with a patch graft or by inserting a bypass graft to reroute the blood flow. The procedure depended on the location and extent of the lesion.

All 17 patients with ear noises were asymptomatic after operation; 16 of the 17 patients with insufficient blood flow to the arm survived the operation and were asymptomatic, although symptoms recurred in one of these patients nine months later. Of the 292 patients, results 7 to 14 days after operation showed that 137 were asymptomatic, 61 were improved, and 64 were unchanged. Eight patients were worse and 22 died. Six months to 7 years later, followup studies on 252 of the 292 patients showed that 142 were asymptomatic, 30 were improved, 32 were unchanged, and 17 had died.

These studies were reported by Drs. E. Stanley Crawford, Michael E. DeBakey, George C. Morris, Jr., and William S. Fields, from the Cora and Webb Mading Department of Surgery and the Department of Neurology, Baylor University College of Medicine, Houston, Tex.

Crawford, E. S., DeBakey, M. E., Morris, G. C., Jr., and Felds, W. S.: Treatment of stroke by arterial reconstructive operation. Southern Med. J. 54: 476–485, May 1961.

MITRAL VALVE-SPLITTING OPERATION SAFER VIA LEFT VENTRICLE

Drs. Andrew G. Morrow and Nina S. Braunwald of NHI's Clinic of Surgery report hemodynamic studies which show that transventricular dilation of the stenosed mitral valve is far superior to the conventional technique of commissurotomy via the left atrium. Transventricular mitral commissurotomy, devised in 1954 by Mr. Andrew Logan of Edinburgh, is almost universally employed in the United Kingdom but has received scant attention in this country. The NHI Clinic of Surgery adopted the technique in 1958 because of inadequate operative results obtained in many patients by the transatrial approach.

As currently practiced in this clinic, mitral commissurotomy involves an initial attempt to open the valve digitally via the left atrium. If this is unfeasible then a two-bladed dilator is inserted through an incision in the heart's apex, passed through the left ventricle, and positioned in the mitral orifice by the surgeon's finger which remains in the atrium to assess the results of dilation.

Although palpation indicated that complete separation of the valve leaflets was easily accomplished and that mitral insufficiency was neither produced nor, if already present, aggravated by transventricular dilation, pre- and post-operative measurements of the abnormal pressure gradient across the valve provided a more objective evaluation of the technique. Such measurements were obtained from 25 patients subjected to transventricular dilation and compared to similar data obtained from 50 control patients whose valves were opened (prior to the adoption of the transventricular technique) digitally or by the use of a knife passed through the atrium.

The studies showed that the reduction of the pressure gradient to less than 8 mm. Hg., considered indicative of satisfactory relief from stenosis, was accomplished in 20 (80 percent) of the patients subjected to transventricular commissurotomy, but in only 26 (52 percent) of the control patients.

"The results of the study indicate that transventricular mitral commissurotomy is a safe and practical technique and effectively relieves mitral obstruction with minimal risk," concludes Drs. Morrow and Braunwald. They also state that the technique will undoubtedly be more widely used as its advantages become better known.

Morrow, A. G. and Braunwald, N. S.: Transventricular mitral commissurotomy; surgical technique and a hemodynamic evaluation of the method. J. Thor, Cardiov. Surg. 41: 225–235, February 1961.

NEW TECHNIQUE TRACES HEART'S CONDUCTION SYSTEM DURING OPEN-HEART SURGERY

Instrumentation and techniques devised by NHI grantees may eventually provide heart surgeons with a practical, reliable means of identifying and accurately locating the specialized conduction system of the heart during open-heart surgery. The instrumentation and results of animal studies using it are reported by Drs. W. A. Bormes, W. C. Gorman, K. L. Kayser, and Derward Lepley, Jr., of Marquette University.

One of the hazards attending surgery to correct ventricular septal defects is that the surgeon may inadvertently damage the specialized conduction system. The bundle of His and the left and right bundle branches, which run down the ventricular septum from the A-V node, are especially vulnerable. Damage to either element may cause partial or complete heart block. Since the paths followed by these elements may deviate considerably from normal in congenital heart disease, the heart surgeon needs a practical, reliable method for locating them. The approach described shows promise of ultimately filling this need.

The technique takes advantage of the fact that the specialized conduction system of the heart offers considerably less resistance to the flow of nerve impulses than does the heart muscle proper. The instrumentation consists of a detector probe containing two wires, whose uninsulated tips are 1 millimeter apart. The wires from the probe are connected to a Wheatstone bridge, an electronic circuit that measures electrical resistance. When balanced for any specific resistance, the bridge is thrown out of balance by either an increase or a decrease in resistance.

In practice, the bridge is balanced for the relatively high resistance of cardiac muscle. This is done by placing the detector probe on some portion of the heart muscle, then adjusting the balance controls until the meter measuring flow across the bridge reads zero. When the probe subsequently encounters the lower resistance offered by some portion of the specialized conduction system, the bridge is thrown out of balance, the hand of the meter is deflected to the right and triggers a contact. The contact activates a speaker which emits an audible signal. The volume of the signal changes with variations in resistance.

Experiments on dogs indicate that the instrument can locate elements of the specialized conduction system with great precision if they lie within 1 millimeter of the surface. However, some elements of the system are buried deeper than this; so the scientists are presently working out modifications to increase the sensitivity of the instrument. Preliminary studies indicate that the proposed changes may triple the effective detection depth.

Bormes, W. A., Gorman, W. C., Kayser, K. L., and Lepley, D., Jr.: The identification of the conduction system of the heart by audiofrequency conductimetry. Surgery 50: 50–57, July 1961.

FIND COMBINATION OF METHODS BEST FOR PROTECTING HEARTS DURING PROLONGED ARREST

The heart can safely tolerate longer periods of anoxic arrest and regains normal function more rapidly when external cooling of the heart is supplemented by intermittent perfusion of the coronary arteries with cold oxygenated blood, NHI studies indicate. These studies, which compared various methods currently used to protect the heart during prolonged anoxic arrest, are reported by Drs. P. A. Ebert, L. J. Greenfield, W. J. Austen, and A. G. Morrow of the NHI Surgery Branch.

Anoxic arrest, in which the heart is stilled by intermittently clamping the aorta, is widely used in open-heart procedures to correct acquired defects of the aortic valve. Although considerably safer than cardiac arrest induced by chemical agents such as acetylcholine or potassium citrate, anoxic arrest becomes hazardous if extended beyond 20–30 minutes. In severely diseased hearts the time available to the surgeon may be considerably shorter.

Since surgical procedures such as partial or total replacement of the aortic valve may require longer than 30 minutes, a number of techniques have been devised for protecting the heart during these prolonged periods of arrest. These include: (1) intermittent perfusion of the coronary arteries with oxygenated blood; (2) cooling the heart by applying ice in saline directly to the heart's external surface; (3) external cooling plus intermittent coronary perfusion with cold Ringer's lactate solution; and (4) external cooling plus intermittent coronary perfusion with cold oxygenated blood.

The NHI scientists evaluated and compared these techniques in dogs subjected to anoxic arrest for periods of 20–45 minutes. Then assessed the relative effectiveness of the techniques by comparing ventricular function curves obtained before arrest with similar curves obtained after a postarrest recovery period of 20 minutes. No drugs were given during this period, but defibrillation procedures were carried out, if needed.

The most effective of the techniques was external cooling supplemented by coronary infusions of cold oxygenated blood. Even after 45 minutes of arrest the hearts showed no significant depression of function. External cooling offered some protection, but the hearts showed moderately severe depression after 30 minutes of arrest. The infusions of cold Ringer's lactate solution did not appear to confer any significant extra protection over external cooling. Infusing the normothermic heart with oxygenated blood was least effective: all of the hearts showed complete depression of function after 30 minutes of arrest.

The scientists conclude that external cooling plus infusions of cold oxygenated blood is the procedure of choice. They point out that metabolism continues even in the bypassed, completely arrested heart. Cooling the heart reduces its metabolic requirements enough so that these can be met adequately by the infusions of cold blood. In addition, this method protects against the possibly harmful effects of uneven cooling or a rise in temperature once hypothermia has been initiated. The infusions of cold blood cool the heart uniformly and the external cooling maintains the temperature.

Ebert, P. A., Greenfield, L. J., Austen, W. J., and Morrow, A. G.: An experimental comparison of methods for protecting the heart during aortic occlusion. Ann. Surg. (in press).

HEART OUTPUT DETERMINED BY SINGLE INJECTIONS OF KRYPTON 85

When radioactive krypton (Kr^{85}) is introduced into the bloodstream, it is largely eliminated during a single trip through the circulation. The gas is cleared either by the lungs or by diffusion into the body tissues. These properties of Kr^{85}, and the ease with which its concentrations in blood or air can be measured, have made it a useful agent for measuring cerebral blood flow, for diagnosing and assessing circulatory shunts, and for other circulatory measurements. Drs. W. P. Cornell, E. Braunwald, and E. C. Brockenbrough, of the NHI Cardiology Branch, report that these features of Kr^{85} also make it a promising agent for determining heart output in certain conditions.

Dye techniques may give inaccurate measures of heart output in cases of congestive failure or valvular regurgitation (backflow of blood through leaky valves). Some of the dye injected into the heart will remain there and some will be recirculated to the heart. Since Kr^{85} has little recirculation, it can be used satisfactorily in these cases. This property makes possible the use of Kr^{85} for separate measurements of left and right ventricular outputs in patients with circulatory shunts. From this data the magnitude of the shunt can be determined. The Kr^{85} technique is simpler than standard dye techniques, requiring less blood, fewer instruments, and less calculation. The gas may be injected (via catheter) into the left side of the heart and its concentration measured in a single blood sample withdrawn at a constant rate from a systemic artery. It may be injected into a vein and measured in blood withdrawn from the pulmonary artery to determine right heart output.

The accuracy of the Kr^{85} technique was tested in three different series of experiments. In two of these series (in a circulatory model and in laboratory animals), the results obtained with Kr^{85} were compared with direct measurements made with a flowmeter. The results were in close agreement: Kr^{85} yielded flow rates that averaged 0.7% less than the actual rates in the circulatory model (maximum difference 11.3%) and values for heart output that averaged 5.2 percent greater than those of the flow rate meter in the laboratory animals, with a maximum difference of 26.1 percent.

When compared with dye dilution techniques in patients, the Kr^{85} technique yielded heart output values averaging 1.5 percent greater. The maximum difference was 11.0 percent.

Cornell, W. P., Braunwald, E., and Brockenbrough, E. C.: Krypton^{85} in the measurement of cardiac output by the single injection indicator-dilution technic. Fed. Proc. 20: pt. 1, 133, Mar. 1961 (Abstract).

New Knowledge and Methods

ATRIAL "BOOSTER PUMP" ACTION IMPORTANT FACTOR IN HEART PERFORMANCE, OUTPUT

NHI studies indicate that the function of the atrium as a "booster pump" for ventricular filling importantly affects ventricular performance and heart output. They also suggest that atrial failure may be a more important factor in congestive heart failure than previously supposed.

The "booster pump" action of the atrium serves to fill the ventricle adequately without the necessity of unduly high venous blood pressure. When the atrium contracts vigorously and efficiently, it propels a larger volume of blood into the ventricle. Being presented with more blood, the ventricle pumps more blood. Its stroke work also increases because the increased volume elongates its muscle fibers and causes them to contract more forcefully. Moreover, the vigorous atrial contraction, by emptying the atrium more completely, leaves in its wake a lower pressure to be overcome by the venous blood that fills the atrium during its relaxation phase.

NHI scientists have studied how much factors as heart rate and autonomic nerve stimulation, by altering the activity of this booster pump, also affect ventricular performance and heart output. The studies were carried out by Dr. S. J. Sarnoff, J. P. Gilmore, and Jere H. Mitchell, of the NHI Laboratory of cardiovascular physiology. Their findings were reported by Dr. Mitchell at the annual meeting of the American College of Cardiology held in New York.

The studies showed that, as heart rate was increased, the duration of the ventricular pumping stroke (systole) increased relative to the total cardiac cycle while the time available for the ventricle to relax and receive blood from the atrium decreased steadily. Atrial contraction thus tended increasingly to encroach on ventricular contraction, and was eventually taking place partially or even completely against a closed mitral valve.

As a result, mean atrial pressure rose. Since mean atrial pressure must be exceeded in moving blood into the atrium, this increased the toll levied on the venous system for atrial filling. However, because of dwindling atrial pumping efficiency, less blood was actually being moved into the ventricle.

At any given heart rate, the action of the atrial booster pump was increased by sympathetic nerve stimulation. This shortened the duration of atrial and ventricular contraction relative to the total cardiac cycle and thus effectively increased the time available for adequate ventricular relaxation and filling.

Vagal stimulation, however, decreased the pumping action of the atrium by depressing the vigor of its contraction. Again mean atrial pressure rose (from the larger volume of blood still remaining in the atrium after its contraction), but again less blood was moved into the ventricle.

These findings suggest that failure of the atria, as well as the ventricles, may be an important factor in congestive heart failure. The mean atrial pressure would be higher as atrial pumping action declined, and this would increase the back pressure in the venous feed lines. Thus, atrial failure could contribute to the elevated systemic venous pressure and to the pulmonary edema that often accompany congestive heart failure.

Sarnoff, S. J., Gilmore, J. P., and Mitchell, J. H.: The transport function of the atrium: factors influencing the relation between mean left atrial pressure and left ventricular end-diastolic pressure. Amer. J. Card. (in press).

NHI STUDIES DEMONSTRATE THAT STARLING'S LAW IS OPERATIVE IN MAN

For many years Starling's Law of the heart has been widely used as a major physiological premise in explaining how heart output is modified in accordance with the varying circulatory demands of the body. The validity of this law in certain experimental animals has been well established; however, its applicability in humans has been a far more controversial matter. Studies conducted by Drs. Eugene Braunwald, C. J. Frahm, and John Ross, Jr., of the NHI Cardiology Branch, have now provided evidence to confirm a concept previously an article of faith to some, a bone of contention to others: Starling's Law is operative in man and is an important determinant of heart output.

Starling's Law states that heart output can be increased by increasing its filling pressure. This produces greater elongation of the heart muscle fibers. Since muscle fibers contract more forcefully from longer fiber lengths (up to a point), the vigor of heart contraction is enhanced and its output per stroke increased.

The studies were carried out in six subjects apparently free from cardiovascular disease. The means for increasing venous return was a transfusion of 1,500 ml. of the subject's own blood, previously obtained by several phlebotomies carried out over 7–10 days.

A ganglionic blocking agent was infused throughout the procedure to reduce the activity of the autonomic nervous system. This was necessary because autonomic stimuli can profoundly affect heart contractility independent of the Starling mechanism and can thus obscure its operation. They can also affect blood pressure and resistance to blood flow by altering the caliber of blood vessels. Previous studies had shown that, without autonomic blockade, transfusions set off reflexes from pressure-sensitive receptors that largely negated the effects of those transfusions on venous return and heart filling pressure.

The NHI scientists measured heart output and pressures in the brachial artery, left ventricle, and esophagus before transfusion; and then at intervals of 10–15 minutes during the 30–50 minute transfusion period. These data, and the measures of ventricular performance calculated from them, showed that the transfusions increased venous return and produced a striking elevation in left ventricular filling pressure. This augmented left ventricular performance; heart output per pumping stroke and per minute increased, as did left ventricular work, power, and rate of ejection of blood. The transfusions were accompanied by significant increases in heart rate in only two of the six subjects.

These findings indicate that ventricular filling pressure importantly affects ventricular contraction, and that Starling's Law, while subject to amendments, is not likely to be repealed in man.

Braunwald, E., Frahm, C. J., and Ross, J., Jr.: A study of ventricular function in man. Fed. Proc. 20: pt. 127, Mar. 1961 (Abstract).

CAROTID REFLEXES AFFECTING VENOUS CALIBER IMPORTANT IN HEART PERFORMANCE

The carotid sinus, a special pressure sensitive receptor (baroreceptor) located where the carotid artery branches in the neck, reacts to changes in carotid pressure with reflexes to compensate those changes. When carotid pressure falls, it initiates reflexes via the sympathetic (excitor) nerves which raise blood pressure by increasing heart rate and heart output per pumping stroke, and by constricting the arterioles. Conversely, when carotid pressure rises, it reflexly lowers blood pressure by reducing heart rate and output and by dilating the arterioles.

NHI studies indicate that carotid sinus reflexes also alter the distensibility of the venous bed, and that these changes are great enough to importantly affect heart performance. These studies are reported by Drs. John Ross, Jr., Charles J. Frahm, and Eugene Braunwald of the NHI's Cardiology Branch.

They found that carotid hypotension, produced experimentally in animals, caused the carotid sinus to initiate reflexes constricting the veins, thereby reducing the capacity of the venous bed and increasing the amount of blood returning to the heart. This substantially increases the heart's filling pressure and acts to increase heart output in accordance with Starling's Law. Experimental carotid hypertension resulted in dilation of the venous bed, increasing its capacity, reducing venous return, and thereby acting to reduce heart output.

Effects similar to those produced by carotid hypotension were also produced by infusions of the catechol amines epinephrine and norepinephrine. Thus it appears that changes in venous distensibility are an important means by which the reflex mechanisms of the baroreceptor system and the hormonal mechanisms of the adrenal glands modify heart performance in accordance with the ever-changing circulatory demands of the body.

Ross, J., Jr., Frahm, C. J., and Braunwald, E.: Influence of carotid baroreceptors and vasoactive drugs on systemic vascular volume and venous distensibility. Circulat. Res. 9: 75–82, Jan. 1961.

COLLAGEN AND ELASTIN CONTENT OF THE LUNG NOT ALTERED IN PULMONARY EMPHYSEMA

Pulmonary emphysema does not result from any primary dissolution or loss or lung collagen or elastin, according to findings reported by Drs. J. A. Pierce, J. B. Hocott, and R. V. Ebert, NHI grantees at the University of Arkansas Medical Center.

Pulmonary emphysema is becoming an increasingly common respiratory disease. In this disease, whose pathogenesis is obscure, the lungs are enlarged and chronically hyperinflated. However, because the walls of many air sacs (alveoli) of the lung are destroyed, its actual surface area for gas exchange is decreased. The retractive force of the lung is also diminished as a result of loss of lung elasticity, and this is associated with an increase in residual volume.

The distortion of lung structure and the loss of lung elasticity found in emphysema have been attributed by many investigators to reductions in lung connective tissue, composed chiefly of the proteins collagen, elastin, and reticulin. This concept is challenged by the findings of Dr. Elbert and coworkers.

The scientists analyzed and compared the collagen and elastin content of lungs taken at autopsy from patients with severe emphysema with that of lungs from patients with no clinical evidence of the disease. Insofar as possible, the control lungs were from subjects whose ages at death corresponded closely with those of the subjects with emphysema, since againg has been reported to alter lung structure and to increase its elastin content.

The analyses revealed no significant differences between the two groups of specimens in (1) the percentage of collagen or elastin per unit weight of connective tissue; (2) the ratio of collagen to elastin; or (3) the valine and hydroxyproline content of the elastin fraction. (These amino acids are characteristic of elastin.) Neither was there any relationship between the severity of damage produced by emphysema in any given tissue sample and the amount of collagen and elastin it contained nor in its ratio of collagen to elastin.

The scientists conclude that there are no gross quantitative differences in connective tissue content between normal and emphysematous lungs. However, they point out, these measurements afford no index of the distribution of connective tissue among specific lung elements; nor do they shed any light on the physiological quality of that tissue. By altering the quality of distribution of lung connective tissue, emphysema could cause profound changes in lung function without affecting its total connective tissue content.

Pierce, J. A., Hocott, J. B., and Ebert, R. V.: The collagen and elastin content of the lung in emphysema. Ann. Intern. Med. 55: 210–222, Aug. 1961.

ANTIDIURETIC HORMONE ACTION MAY INVOLVE ATP DERIVATIVE AS BIOCHEMICAL MIDDLEMAN

NHI studies suggest that the action of antidiuretic hormone may be mediated by adenosine 3′, 5′-phosphate (3′, 5′-AMP for short. Antidiuretic hormone may stimulate the production of this compound from the high-energy substance ATP in susceptible tissues, and this derivative may be directly responsible for the increased water permeability observed in these tissues when antidiuretic hormone is present.

Antidiuretic hormone (ADH) aids the kidney in maintaining fluid balance by regulating the renal urine concentrating mechanism. This mechanism gears fluid output to fluid intake so that the body neither becomes waterlogged nor dehydrated when fluid intake fluctuates widely.

ADH regulates this mechanism by its action on the latter half of the kidney tubule. Without ADH, this segment is relatively impermeable to water. When fluid intake is low, ADH, released from the pituitary, acts to conserve water by making possible its reabsorption in this segment. The result is a smaller volume of more concentrated urine. When fluid intake is high, little or no ADH is released, little water reabsorption takes place in this segment, and the unneeded water escapes in a larger volume of more dilute urine.

This site of action of ADH has been well established, but the mechanisms by which it affects water permeability had not been defined. Drs. Jack Orloff and J. S. Handler, of the NHI Laboratory of Kidney and Electrolyte Metabolism, set out to learn whether ADH might not act indirectly through a biochemical mediator.

A compound that keeps turning up in tissues when and where a number of hormones are at work is 3′, 5′–AMP. The release of adrenal hormones by ACTH, the release of glucose from liver by epinephrine, the stimulation of the heart by catechol amines: all appear to be accompanied by the accumulation of 3′, 5′–AMP in the affected tissues.

Since ADH shares with ACTH the ability to release adrenal hormones and with epinephrine the ability to release liver glucose, the scientists reasoned that 3′, 5′–AMP might also be involved in the mechanism of action of ADH. They studied the effects of ADH and 3′, 5′–AMP on the toad bladder. Others had shown that ADH affects the water permeability of this organ.

The study showed that 3′, 5′–AMP, used alone brought about the same increase in bladder permeability as did ADH alone. When the two were used together, their effects on water permeability were additive. Further, the effects of either or both were enhanced when the inactivation of 3′, 5′–AMP was blocked with the drug theophylline.

These findings suggest that ADH affects the permeability of the toad bladder, and perhaps the renal tubule, by stimulating the production and accumulation of 3′, 5′–AMP. Studies aimed at providing more direct evidence for this hypothesis are being carried out in collaboration with Dr. E. W. Sutherland of Western Reserve University, Cleveland.

Orloff, J. and Handler, J. S.: Vasopressinlike effects of adenosine 3′, 5, phosphate (cyclic 3′, 5′–AMP) and theophylline in the toad bladder. Biochem. Biophys. Res. Commun. 5: 63–66, May 15, 1961.

RIBONUCLEASE REORGANIZATION DEMONSTRATES IMPORTANCE OF AMINO ACID SEQUENCE

Enzymes, the protein executives that expedite nearly all of the body's biochemical business, may also share with their human counterparts the capacity for spontaneous reorganization. Drs. Christian B. Anfinsen, Edgar Haber, and Fred H. White, of the NHI Laboratory of Cellular Physiology and Metabolism, recently reported that ribonuclease, after being subjected to a chemical shakeup severe enough to disrupt its normal spherical shape and to eliminate its enzymatic activity, is able to regain both properties spontaneously under suitable chemical conditions.

Enczymes appear to be made in the cell under the control of RNA. This substance, in turn, is probably constructed according to coded instructions in the DNA of the cell nucleus. The RNA carries the directions for stringing the proper number of the proper amino acids into the proper sequence to form the protein chain or chains of the enzyme. DNA, which is able to duplicate itself, appears to be the repository of all of the body's genetic information.

The activity of enzymes depends not only upon the basic structure of their protein chains, but also upon the manner in which these chains are coiled or folded in three dimensions. Drs. Anfinsen, Haber, and White were concerned with whether this geometric property is also determined by the RNA blueprint or whether it might be predetermined, at least in part, by the amino acid sequence of the chains.

The enzyme ribonuclease consists of a single chain of 124 amino acids coiled into a roughly spherical shape. It is held in this configuration by disulfide bridges connecting portions of the chain at four points. The scientists "uncoiled" this chain, using reducing agents that selectively break these disulfide bridges but not the chain itself.

The resulting molecule exhibited none of the enzymatic activity of the native ribonuclease. However, in the presence of molecular oxygen and suitable conditions of alkalinity, the uncoiled chain was able to reorganize spontaneously, regaining both its original configuration and its lost activity.

This finding indicates that, in many cases, the amino acid sequence alone may be enough to determine the secondary and tertiary structure of an enzyme. This is good news to protein chemists interested in enzyme synthesis. Protein chains of predetermined length and amino acid sequence can be synthesized in the laboratory, but the task of moulding these chains into the proper configuration to confer enzymatic activity upon them appeared to pose far more formidable problems.

Haber, E. and Anfinsen, C. B.: Regeneration of enzyme activity by air oxidation of reduced subtilisin-modified ribonuclease. J. Biol. Chem. 236: 422–424, Feb. 1961.

White, F. H., Jr.: Regeneration of native secondary and tertiary structures by air oxidation of reduced ribonuclease. J. Biol. Chem. 236: 1353–1360, May 1961.

ENZYMATIC DUPLICATION OF EFFORT MAY CONTRIBUTE TO PRODUCTION EFFICIENCY

In one of the enzymatic assembly lines of *Escherichia coli*, this microbe has three enzymes doing the same job. All attach a single phosphate group onto the amino acid, aspartic acid. However this apparent duplication of effort may be essential to the efficiency of that particular assembly line, according to a collaborative study conducted by Dr. E. R. Stadtman, of the NHI Laboratory of Cellular Physiology and Metabolism; and Drs. G. N. Cohen and Gisele LeBras, of the Pasteur Institute, Paris.

The scientists point out that *E. coli* may need more than one aspartokinase because the aspartyl phosphate that they produce is necessary for the synthesis of three amino acids: lycine, threonine, and methionine.

The rate at which substances are synthesized by the cell is geared to cellular needs by two mechanisms called "feedback" and "repression." Both restrain enzyme systems from glutting the cellular market almost literally by drowning the enzyme system in its own surplus.

In "feedback," the surplus product curtails further production by inhibiting usually the first enzyme of the system. This inhibition may be competitive or noncompetitive. In competitive inhibition, the surplus product is similar enough in structure to the enzyme's normal substrate to compete with the substrate for that enzyme's active sites. In the noncompeitive inhibition, the surplus product may combine with the enzyme and then refuse to let go. The enzyme, unable to accommodate further substrate is, effectively inactivated.

In "repression," the surplus product curtails further production by effectively reducing the enzymatic labor force. It inhibits the synthesis of enzymes involved in that particular metabolic pathway.

However, in situations where a single enzyme catalyzes the first step of a metabolic sequence leading to the formation of more than one product, a surplus of any one could also cause curtailment of production of the others. Since aspartyl phosphate is needed to make three amino acids in *E. coli*, the presence of three aspartokinases prevents a temporary surplus of one amino acid from possibly leading to cellular shortages of the other two.

The scientists found that one aspartokinase was inhibited only by a surplus of the amino acid end product lysine, another only by threonine, and the third by homoserine. Lysine appeared to inactivate its aspartokinase by combining tightly with it. Threonine inhibited its aspartokinase by competing with aspartic acid for the enzyme's active sites. The homoserine-sensitive aspartokinase, present only in very small quantities, was not studied in detail.

Feedback appeared to be a factor in the inhibition of both of the aspartokinases investigated. The repression mechanism did not appear to operate in the inhibition of the threonine-sensitive enzyme, but was involved in the inhibition of the lysine-sensitive enzyme. The latter was not formed at all when *E. coli* was grown in the presence of lysine.

Stadtman, E. R., Cohen, G. N., and LeBras, G.: Feedback inhibition and repression of aspartokinase activity in Escherichia coli. J. Biol. Chem. (in press).

ADRENALINE OUTPUT MAINTAINED DESPITE TOTAL ADRENALECTOMY, CLINICAL STUDIES SHOW

National Heart Institute grantees studied adrenaline excretion in the urine of ten patients before and after unilateral and bilateral total adrenalectomy and noted significant decrease in adrenaline output in only three of the patients.

Adrenaline is secreted into the bloodstream by the chromaffin tissue of the adrenal medulla. By measuring the amount of adrenalin excreted in the urine, scientists can obtain an indication of the amount of adrenaline circulating in the body. However, very few studies have been made on the excretion of adrenaline after bilateral total adrenalectomy in man.

NIH grantees Drs. A. F. De Schaepdryver from the J. F. Heymans Institute of Pharmacology, University of Ghent, Belgium, and W. Smets from the Department of Surgery, Bordet Cancer Institute, University of Brussels, Belgium, studied 10 women suffering from cancer. They collected urine samples before adrenalectomy, in the first week after unilateral total adrenalectomy, and after subsequent removal of the second adrenal. (Patients were given cortisone after bilateral total adrenalectomy.

Unilateral total adrenalectomy resulted in decreased adrenaline output in only three patients. Estimations of adrenaline output made as long as 9 months after bilateral total adrenalectomy showed a significant decrease in only three patients.

These findings support the theory that adrenaline is secreted by tissues other than the adrenal medulla. Chromaffin tissue has been found in other parts of the body, but scientists have been unable to show that such tissues are capable of secreting adrenaline.

De Schaepdryver, A. F., and Smets, W.: Urine output and excretion of catecholamines after bilateral total adrenalectomy in man. Arch. Int. Pharmacodyn. 131: 467–473, May 1, 1961.

GAS CHROMATOGRAPHY APPLIED SUCCESSFULLY TO SEPARATE AMINO ACID MIXTURES

The successful application of gas chromatography for the separation of amino acid mixtures is reported by NHI grantees Donald E. Johnston, Sara J. Scott, and Alton Meister of Tufts University. The technique devised by these National Heart Institute grantees has been successful in separating 35 amino acids, including 18 of the 20 amino-acid constituents of proteins. The technique is fast and can be used to analyze samples weighing much less than a millionth of a gram.

In gas chromatography, the mixture to be separated is injected into an analytical column, vaporized, and carried through the column on a stream or argon or helium (called the gas phase). The column contains a greaselike solvent (called the liquid phase), usually in the form of a thin film on inert, finely divided particles with which the column is packed. The mixture components are soluble to some extent in both phases. However, the degree to which any component favors one phase or the other is determined by chemical structure, and thus is different for each component.

This variation affords the means of separating the components. Those showing the greater affinity for the gas phase pass rapidly through the column; those with the greater affinity for the liquid phase pass through more slowly.

Amino acids had proved difficult to separate by gas chromatography because their highly polar amino and acid groups made them relatively indifferent to both phases, and also prone to decompose at normal column temperatures. Using simple chemical procedures requiring less than an hour, the grantees masked both of these polar groups. This involved adding a two carbon acetyl fragment to the amino group and a suitable alcohol to the acid group. The esters made with amyl alcohol were generally most suitable for gas chromatography.

These derivatives could be separated effectively and fairly rapidly (most within 45 minutes) by using a 2- to 8-foot column whose inert particles were coated with a thin film of polyethylene glycol. The temperatures used ranged from 125–148° and produced no noticeable decomposition. Those derivatives having long retention times could be separated more rapidly by using a shorter column containing a lower percentage of solvent.

The technique is not yet applicable to the complex analysis of protein fragments, but shows promise of developing eventually into a valuable addition to presently available techniques. It could prove especially useful where only very small samples are available or where a large number of analyses are required.

Johnston, D. E., Scott, S. J., and Meister, A.: Gas-liquid chromatography of amino acid derivatives. Anal. Chem. 33: 669–673, May 1961.

HIGHLY SPECIFIC ACTION OF ANTIDEPRESSANT DRUG DUE TO METABOLITE

National Heart Institute scientists have shown that the antidepressant drug imipramine (Tofranil, Geigy) is able to counteract, and even to "reverse", the syndrome of central nervous system depression produced by reserpine and reserpine-like drugs. This syndrome includes contraction of the pupils, drooping eyelids, diarrhea, decreased responsiveness to sensory stimuli, decreased locomotor activity, and other signs of sedation.

Multiple doses of imipramine, when given to test animals well in advance of reserpine or similar-acting drugs, not only prevented these drugs from eliciting sedation, but actually appeared to reverse their effects. The animals now exhibited hyperactivity, extreme curiosity, and other signs of stimulation. These stimulatory effects could not be produced by imipramine alone. Further, in animals given imipramine and then a short acting reserpine-like drug, the stimulatory effects subsided when the action of the reserpine-like drug had ceased, even if imipramine was still present in significant amounts.

The considerable delay in onset of imipramine's antidepressant action made the scientists suspect that a drug metabolite might be the active principle. They subsequently found that a single methyl ($-Ch_3$) group was removed from imipramine in the course of its metabolism. The metabolite, desmethylimipramine, mediated all of the antidepressant effects of imipramine. The parent compound, in fact, produced mild sedative effects and actually interfered with the antidepressant action of its metabolite.

Desmethylimipramine is the prototype of a new kind of antidepressant drug that is almost specific for depressed states. A potent, fast-acting compound that is highly effective in depressed patients, desmethylimipramine has little or no effect in normal subjects.

The drug's mechanism of action is still obscure. It does not prevent the depletion of brain amines by reserpine, believed responsible for reserpine's sedative effects; nor does it inhibit monoamine oxidase, as do a number of other antidepressant drugs. The NHI scientists are currently investigating two possibilities: the drug may reduce parasympathetic activity by inhibiting the neurohormonal activity of brain serotonin, or it may enhance the effects of free norepinephrine at central adrenergic receptor sites.

The isolation and identification of desmethylimipramine was reported by Drs. J. R. Gillette, J. V. Dingell, F. Sulser, R. Kuntzman, and B. B. Brodie, of the Laboratory of Chemical Pharmacology; the pharmacological studies were reported by Drs. F. Sulser, J. Watts, and B. B. Brodie, of the same laboratory.

Gillette, J. R., Dingell, J. V., Sulser, F., Kuntzman, R., and Brodie, B. B.: Isolation from rat brain of a metabolic product, desmethylimipramine, that mediates the antidepressant activity of imipramine (Tofranil). Experientia 17: 417–418, 1961.

Sulser, F., Watts, J., and Brodie, B. B.: On the mechanism of antidepressant action of imipramine-like drugs. Ann. N.Y. Acad. Sci. (in press).

STUDIES AIMED AT CORRELATING FIBRINOGEN'S MOLECULAR STRUCTURE, FUNCTION

Chemical "dissection" of fibrinogen by protein-digesting enzymes is yielding important information about fibrinogen's physico-chemical structure and molecular sites susceptible to chemical activity, report National Heart Institute scientists.

Fibrinogen, a plasma protein essential for blood coagulation, is converted by thrombin into fibrin, whose molecules then link together in long chains to form the blood clot. From the known amino acid composition of fibrinogen, the NHI scientists had previously calculated the total number of chemical bonds within the molecule that are susceptible to breakdown by various enzymes and chemical reagents.

In the currently reported studies, sequential steps in the enezymatic breakdown of fibrinogen by trypsin were examined by measuring changes in viscosity and in the amount of alkali required to maintain a constant pH (an index of the number of bonds split), and by optical rotation and sedimentation in the ultracentrifugee. The studies showed that trypsin rapidly splits the fibrinogen molecule into three large, nearly spherical fragments, each having a molecular weight of 102,000. Initial fragmentation, which required the rupture of 70 peptide bonds, was followed by a period of slow degradation into products of low molecular weight and accompanied by the liberation of non-protein nitrogen.

In preliminary attempts to locate the molecular sites essential for clot formation, fibrinogen was subjected for varying time intervals to digestion by trypsin, chymotrypsin, or plasmin, and its clottability in the presence of thrombin determined. (Both trypsin and chymotrypsin are digestive enzymes secreted by the pancreas and not normally found in the blood; whereas plasmin is a plasma component believed essential for maintaining blood fluidity.)

The scientists found that the clottability of fibrinogen treated with trypsin disappeared even before the large fragments were liberated, suggesting that the essential bonds in the fibrinogen molecule are split at a faster rate than those connecting the fragments. Fragments liberated by chymotrypsin or plasmin, on the other hand, retained a limited ability to react with thrombin although actual clotting did not occur. Further studies of this limited reaction, uncomplicated by clotting, may lead to increased understanding of events initiating clot formation in the body.

These studies, reported by Dr. Elemer Mihalyi and Mr. Jamie E. Godfrey of the NHI's Laboratory of Cellular Physiology and Metabolism, are part of a program of basic research aimed at determining the molecular composition and structure of various proteins and at correlating this molecular architecture with physiological function.

Mihalyi, E. and Godfrey, J. E.: Fragmentation of bovine fibrinogen by trypsin. Fred. Proc. 20: part 1, 385, Mar. 1961. (abstract).

NHI SCIENTISTS DEVISE MORE PRECISE DIAGNOSTIC TEST FOR HYPERPARATHYROIDISM

Scientists of the NHI clinical endocrinology branch have devised a new clinical test for hyperparathyroidism that affords a more precise diagnosis of this disorder than do tests used previously. The new test involves feeding a diet low in calcium and phosphorus over a period of 13 days and giving aluminum hydroxide orally during the last 10 days of the regimen. The diagnosis of hyperparathyroidism is established if the subject's urinary calcium exceeds 250 mg. per day during the test period.

The parathyroids secrete a hormone which exerts profound effects on calcium and phosphorus metabolism. In hyperparathyroidism, excessive amounts of this hormone usually cause increased serum levels of calcium and increased loss of calcium in the urine. These changes, which can lead to kidney stones, impaired kidney function, and increased susceptibility of the bones to fractures, are usually accompanied by low serum phosphorus levels and in many cases by increased serum levels of the enzyme alkaline phosphatase, the result of deranged bone metabolism.

The diagnostic criteria normally used to establish hyperparathyroidism are excessive serum calcium, excessive urinary calcium, and abnormally low serum phosphorus. However, all of these criteria are not met in many cases of hyperparathyroidism; and some of them, notably hypercalcemia, may be due to other causes. Thus, this disorder often presents a ticklish problem of differential diagnosis.

The new test appears to overcome many of these problems. It was evaluated in 10 normal controls and in 18 patients with established hyperparathyroidism, but only 4 of which met all of the diagnostic criteria above. When put on the test regimen, however, all 18 patients exhibited abnormally high urinary outputs of calcium—defined as a rise in urinary calcium above 250 mg. per day regardless of values of serum calcium or of serum and urinary phosphorus. In contrast, the urinary calcium of the normal controls never exceeded 230 mg. per day. The specificity of the new test was further verified by the observation that urinary calcium reverted to normal in five patients tested after surgical correction of their hyperparathyroidism, whereas it became abnormal in controls tested after they had been given parathyroid hormone.

The aluminum hydroxide administered as part of the test effectively converts a low phosphorus intake into a very low one by interfering with the absorption of phosphorus from the intestine. It also appears to enhance calcium absorption in hyperparathyroid subjects to a much greater extent than in normal subjects. This action of the aluminum hydroxide, though not completely understood, appears to be chiefly responsible for the specificity of the test.

The new test, especially when used in combination with the calcium infusion test previously found to be a reliable means of diagnosis, allows diagnosis of hyperparathyroidism with greater accuracy and precision than heretofore possible. The new test was devised by Drs. Pacita Pronove, Norman H. Bell, and Frederic C. Bartter.

Pronove, P., Bell, N. H., and Bartter, F. C.: Production of hypercalciuria by phosphorus deprivation on a low calcium intake: a new clinical test for hyperparathyroidism. Metabolism 10:364–371, May 1961.

ROLE OF NOREPINEPHRINE IN SYMPATHETIC GANGLIA CLARIFIED BY NHI WORK

Acetylcholine is one of the most important and ubiquitous of the body's neurohormones. These are chemical substances whose release is triggered by nerve impulses and whose function is to bridge the "gaps," or synapses, between nerves at nerve junctions (such as ganglia) and between nerve endings and their effector organs.

Acetylcholine is believed to be the nerve-impulse transmitter at many of the body's nerve junctions and nerve terminals. Thus, some sort of control mechanism for this neurohormone has often been postulated in attempts to explain the tight control maintained by the body over its nervous system. Recent studies by Drs. E. Costa, E. M. Reyzin, R. Kuntzman, S. Spector, and B. B. Brodie, of the NHI laboratory of chemical pharmacology, suggest that norepinephrine may participate in one such mechanism.

Norepinephrine is an amine released from the adrenal glands in response to stress, exercise, or other factors calling for increased metabolic activity. It is also a neurohormone that acts between nerve ending and effector organ in many sympathetic nerves.

However, acetylcholine is believed to handle the nerve-to-nerve traffic at the sympathetic ganglia. Thus the findings of others that sympathetic ganglia also contain fairly large quantities of norepinephrine prompted the NHI scientists to investigate what it was doing there.

Accordingly, animal studies were undertaken to compare the transmission of graded electrical stimuli across sympathetic ganglia containing normal amounts of norepinephrine with transmission across these ganglia after their norepinephrine content had been altered by drugs.

The scientists used reserpine to deplete sympathetic ganglia of norepinephrine. Then they applied electrical stimuli of graded strength to preganglionic nerve fibers and measured the potential of the resulting nerve impulses after they had crossed the ganglionic synapses into the postganglionic nerve fibers.

With any given preganglionic stimulus, the potential of the postganglionic impulse increased markedly when ganglionic norepinephrine fell below 15 percent of normal. This indicated that norepinephrine depletion had enhanced nerve-to-nerve transmission.

Even very weak stimuli would now set off all of the ganglionic nerve cells and produce postganglionic impulses of maximum strength. Before norepinephrine depletion, such stimuli had set off so few nerve cells that no measurable postganglionic impulse was produced. Similar enhancement of synaptic transmission was observed after drugs which block the action of norepinephrine were given.

The scientists next used a "combination of ingredients" to determine the effects on synaptic transmission of high ganglionic levels of free norepinephrine. They first administered a drug that blocks the enzymatic destruction of norepinephrine, then used reserpine to liberate the ganglionic stores of the amine.

Since the free amine could now be cleared only by passive diffusion, very high levels persisted for a time in the ganglia. During this time, synaptic transmission was markedly depressed. However, when the free amine had at last diffused away and the ganglia were again depleted of norepinephrine, transmission was again enhanced.

The studies show that norepinephrine as well as acetylcholine is involved in synaptic transmission. Both are apparently released by preganglionic nerve impulses. Acetylcholine acts as the transmitter across the nerve junctions while norepinephrine, in some unknown way, modulates or "damps" its action.

This may well be an important mechanism for buffering large fluctuations in central sympathetic output within carefully prescribed limits.

Costa, E., Revzin, E. M., Kuntzman, R., Spector, S., and Brodie, B. B.: Role for ganglionic norepinephrine in sympathetic synaptic transmission. Science 133: 1822–1823, June 9, 1961.

PRIMARY ALDOSTERONISM DIAGNOSED ACCURATELY WITH ALBUMIN TEST

National Heart Institute scientists have found that infusions of sodium-free albumin provide a simple and reliable diagnostic test for primary aldosteronism. The new test was devised by Drs. B. R. Kliman, N. H. Bell, and F. C. Bartter, of the NHI Clinical Endocrinology Branch.

The new test was evaluated in 17 subjects with elevated aldosterone: 4 sodium-depleted normal subjects, 7 patients with primary aldosteronism, and 6 with secondary aldosteronism. Daily infusion of 50–100 grams of sodium-free albumin caused a sharp drop from control values in the rates of aldosterone secretion and excretion in the normal subjects and patients with secondary aldosteronism. The infusions had little or no effect on these rates in the patients with primary aldosteronism.

The specificity of the new test lies in the fact that aldosterone secretion in primary adosteronism is not affected by changes in blood volume. This is not true of secondary aldosteronism; and the albumin infusions, by expanding blood volume, decrease aldosterone production.

Aldosterone, a hormone from the adrenal cortex, regulates the excretion of sodium and plays an essential role in the maintenance of blood volume and fluid balance. However, excessive amounts of this hormone are produced in many disease states. By causing excessive sodium retention, this hormone may contribute to the excessive fluid retention and edema that accompany many of these disorders.

Primary aldosteronism is usually the result of an adrenocortical tumor or of the excessive prolifieration of otherwise normal adrenocortical tissue (hyperplasia). Secondary aldosteronism may be produced by salt depletion and may result from organic diseases, especially of the liver or kidneys; from congestive heart failure; or from many other disorders.

Aldosteronism may accompany so many diseases that, unless the underlying disease has its own clearly definable symptoms, distinguishing between primary and secondary aldosteronism can pose a difficult diagnostic task. Frequently, exploratory surgery has been required to establish the diagnosis.

Primary aldosteronism appears to be a far more common disorder than previously supposed, and secondary aldosteronism is now a frequently encountered clinical state. Thus the new test—simple, reliable, and safe—fills an important diagnostic need.

Kliman, B. R. and Bartter, F. C.: Albumin infusion; a new test for primary aldosteronism. (Clin. Res. 9; 182, Apr. 1961.) (Abstract.)

SOME BRAIN REGIONS LACK BLOOD-BRAIN BARRIER, STUDIES INDICATE

National Heart Institute scientists conclude that the blood-brain barrier which restricts passage of substances into the brain and cerebrospinal fluid does not exist in special regions of the brain.

Earlier studies by investigators elsewhere had shown that dyes injected intravenously will stain certain special regions of the brain—the neurohypophysis, the adenohypophysis, the area postrema, and the intercolumnar tubercle—but not the brain proper. However, these investigators did not determine whether this reaction was due to an affinity between dye and tissue or to an absence of blood-brain barrier.

Current studies of this reaction were reported by Dr. Cedric W. M. Wilson, presently with the Department of Pharmacology and General Therapeutics, University of Liverpool, England, and Dr. Bernard B. Brodie, NHI Laboratory of Chemical Pharmacology.

Drs. Wilson and Brodie injected into the veins of cats, N-acetyl-4-amino-antipyrine (NAAP) and sulfaguanidine, substances known to mix easily and evenly with the water of tissues without being bound to cellular constituents. They then measured the peneration of these substances into the water spaces of the special brain regions and the rest of the brain.

Shortly after injection, the concentration of the substances was almost as high in the special regions as in the peripheral tissues. It was several hours before the concentration of NAAP or sulfaguanidine in the cerebrospinal fluid or the brain proper approached this level. From these results, it is apparent that these special regions of the brain have little or no barrier to the entrance of these substances.

There are other differences between the special regions and the rest of the brain: the small number of neural cells; a different vascular pattern; and some evidence of a neuroendocrine function.

Wilson, C. W. M., and Brodie, B. B.: The absence of blood-brain barrier from certain areas of the central nervous system. (J. Pharmacol. Exp. Ther. 133:332–334, Sept. 1961.)

Monday, February 19, 1962.

NATIONAL INSTITUTE OF DENTAL RESEARCH

WITNESSES

DR. SEYMOUR J. KRESHOVER, ACTING DIRECTOR, NATIONAL INSTITUTE OF DENTAL RESEARCH

DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

RICHARD L. SEGGEL, EXECUTIVE OFFICER

JOHN E. FITZGERALD, ADMINISTRATIVE OFFICER, NATIONAL INSTITUTE OF DENTAL RESEARCH

DR. LUTHER L. TERRY, SURGEON GENERAL

JAMES F. KELLY, DEPARTMENT BUDGET OFFICER

Object classification

[In thousands of dollars]

	1961 actual	1962 estimate	1963 estimate
11 Personnel compensation:			
Permanent positions	1,042	1,503	1,622
Positions other than permanent	20	48	48
Other personnel compensation	9	10	10
Total personnel compensation	1,071	1,561	1,680
12 Personnel benefits	145	175	183
21 Travel and transportation of persons	66	77	89
22 Transportation of things	10	12	14
23 Rent, communications, and utilities	21	30	31
24 Printing and reproduction	30	4	4
25 Other services	58	105	115
Payment to "National Institutes of Health management fund"	732	915	988
26 Supplies and materials	248	269	292
31 Equipment	832	102	62
41 Grants, subsidies, and contributions	9,268	12,059	13,746
Subtotal	12,481	15,309	17,204
Deduct quarters and subsistence charges	5	5	5
Total obligations	12,476	15,304	17,199

Personnel summary

	1961 actual	1962 estimate	1963 estimate
Total number of permanent positions	181	247	258
Full-time equivalent of other positions	3	7	7
Average number of all employees	160	228	243
Number of employees at end of year	192	244	255
Average GS grade	6. 5	7. 0	7. 1
Average GS salary	$5, 859	$6, 023	$6, 167

Program and financing

[In thousands of dollars]

	1961 actual	1962 estimate	1963 estimate
Program by activities:			
1. Grants and related contracts:			
(*a*) Research	5, 505	7, 436	9, 123
(*b*) Fellowships	798	882	882
(*c*) Training	2, 965	3, 741	3, 741
Total, grants and related contracts	9, 268	12, 059	13, 746
2. Direct operations:			
(*a*) Research	2, 330	3, 224	2, 858
(*b*) Review and approval of grants	243	368	424
(*c*) Administration	116	146	171
Total, direct operations	2, 689	3, 738	3, 453
Total program costs [1]	11, 957	15, 797	17, 199
Change in selected resources [2]	519	−493	
Total obligations	12, 476	15, 304	17, 199
Financing:			
Comparative transfers to other accounts	2, 140		
Unobligated balance lapsing	884	2, 031	
New obligational authority	15, 500	17, 335	17, 199
New obligational authority:			
Appropriation	15, 500	17, 340	17, 199
Transferred to "Operating expenses, Public Buildings Service," General Services Administration (75 Stat. 353)		−5	
Appropriation (adjusted)	15, 500	17, 335	17, 199

[1] Includes capital outlay as follows: 1961, $359,000; 1962, $561,000; 1963, $62,000.

[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1960, $33,000; 1961, $552,000; 1962, $59,000; 1963, $59,000.

Mr. Fogarty. The committee will come to order. We have before us this morning the request of the Dental Institute.

Dr. Kreshover, you are going to testify in Dr. Arnold's place because of the sickness of Dr. Arnold?

Dr. Kreshover. Yes, sir.

Mr. Fogarty. Please proceed.

BIOGRAPHICAL SKETCH OF DR. KRESHOVER

Dr. Kreshover. May I take this opportunity to introduce myself? My name is Seymour J. Kreshover, I was born in New York City 49 years ago. I received my primary and secondary education in the city. I then went on and received my dental degree from the University of Pennsylvania and my medical degree from New York University.

I attended graduate school at Yale University as a Carnegie fellow and received a Ph. D. degree in clinical medicine and pathology. During the Second World War years I served with the Affiliated Yale General Hospital Unit as chief of its dental service.

My hospital and teaching positions have been, briefly, assistant in oral surgery at the Yale School of Medicine, assistant in operative dentistry at the University of Illinois, teaching fellow in histoanatomy at New York University, and more recently, from 1949 to 1956, I served as professor of oral pathology and director of dental research and graduate studies at the Medical College of Virginia in Richmond.

I came to the National Institutes of Health in August 1956, and have served since that date as Associate Director of the Dental Institute. It is my privilege to currently serve as chairman of the Commission on Dental Research of the International Dental Federation and as president elect of the International Association for Dental Research.

General Statement

Mr. Chairman and members of the committee, permit me to say at the outset that the privilege of appearing before you is especially welcome as it provides an opportunity to call attention to a most exciting and productive year in the history of our Institute. I should say also that Dr. Arnold and I both regret his inability to be here.

NEW ACTIVITIES

In introduction to my summary of the full opening statement, being entered for the record, may I express our sense of great pride in the new home we so recently occupied, and the gratitude of our scientists to those, Mr. Chairman, who made possible this important consolidation of our resources and the profitable expansion of our professional staff and research programs. As an example of this progress, I would cite a new research section established recently in the field of protein chemistry, the purpose of which is to provide a clearer basic understanding of the chemical processes involved in the calcification of bones and teeth and an elucidation of the biochemical and enzymatic factors involved in dental decay, periodontal disease, and other related disorders.

Also organized recently was a new clinical program to study the development and function of the mouth, pharynx, and adjacent structures as they perform—or fail to perform—during mastication and speech.

RECENT RESEARCH PROGRESS

Other Institute studies in the field of oral microbiology have shown that not only may dental caries be a specific disease of bacterial origin, but that it is transmissible in character, and causally related in two different animal species to specific micro-organisms. Although it would be premature at this time to apply these findings to man, a major effort is being directed to a clinical evaluation of this new concept of caries.

Another important laboratory investigation has contributed significantly to a better understanding of the mechanism of calculus formation. Utilizing newer approaches of germ-free study, electron diffraction, and X-ray and electron microscopy, sufficient evidence has now been assembled to offer some promise for the ultimate elimination or control of this major contributing factor to periodontal disease.

In our program of human genetics, the Institute has sought to establish a research potential capable of dealing with the broad aspects of genetics. Understandably, however, principal attention has been given to hereditary conditions with oral manifestations. The valuable information gained from this program, particularly as related to the study of selected populations with unique patterns of intermarriage between closely related family groups, has resulted also in a number of fruitful collaborative projects with scientists in other Institutes of the NIH, as well as with scientists in some of our universities such as Howard, Catholic, and Michigan. Through these studies, a considerable store of new information has been derived concerning such abnormalties as malformed teeth, disturbed dental eruption, and diseases of the soft tissues of the mouth associated with eye lesions and renal disorders.

Related epidemiological studies, in cooperation with the ICNND—I believe Dr. Daft will say more about this since it is in his Institute—have also been contributing important data on the patterns of periodontal disease and dental caries in various ethnic groups in foreign countries and other selected populations in the United States. I shall be happy to comment further on this program later on should you desire.

Turning now to the Dental Institute's extramural programs, the past year has seen a continued encouragement and support of fundamental research in the basic and clinical sciences through the grants program. During the year, the number of active grants totaled 455 at 133 institutions in 39 States and territories and 13 foreign countries. Areas receiving particular attention were congenital defects (including cleft lip and palate), peridontal disease and dental caries, and the behavioral sciences as related to public acceptance of various dental health procedures.

FELLOWSHIPS AND TRAINING

The fellowship program, so vital to the objectives we seek, offers to dental graduates and others, the opportunity to receive an educational background in the basic biological sciences as applied to dentistry. Thus qualified, these individuals can assume the important role of full-time researchers and teacher-investigators in our dental schools and other institutions devoted to health care and biomedical and dental research.

The training program, principally directed toward providing educational opportunities in the clinical sciences, is likewise receiving major attention. The considerable progress of this program is evidenced by the 200 individuals now enrolled in already established training centers. In another area of training, programs are being supported in 42 dental schools to provide instruction in the proper use of chairside assistants.

1963 BUDGET

The request for the National Institute of Dental Research in 1963 is $17,199,000. This allowance for 1963 will provide increases of: (1) $1,687,000 to support approximately 40 new research projects and broad program activities; (2) $134,000 for direct research; (3) $51,000 for review and approval of grants; and (4) $23,000 for administration.

Mr. Chairman, I have referred in these brief introductory remarks to but several key accomplishments of the Dental Institute during the past year. These and other items and program areas are discussed in detail and at considerably greater length in the statement submitted for the record. I shall be happy, sir, to answer and discuss any questions you and your committee may have regarding the Institute's program and the related budget request.

Mr Fogarty. Thank you, Doctor. We shall place your more detailed statement in the record at this point.

(The statement follows:)

The following statement will review for this committee progress made by the National Institute of Dental Research in its programs to better the general health of the Nation through research into the cause and prevention of oral diseases.

The oral health needs of the Nation continue to present an increasing challenge to the dental profession. Less than one child in eight now requiring orthodontic treatment can be cared for. Children born with cleft lips and palates are accumulating at a rate of approximately 8,000 per year. Only a fraction of these tragically afflicted children are receiving the optimum of skilled care which is required for their successful rehabilitation. Diseases of the supporting bone and gingival tissues affect at least half of the population by age 50 and almost all by age 65. The magnitude of this problem is apparent from the fact that more than half of all dental extractions are the direct result of periodontal involvement. Dental decay affects more than 9 persons in 10, and the staggering accumulation of untreated teeth far exceeds the capacity for treatment.

The successful resolution of these and a variety of other oral and dental health problems will depend largely upon the development of more effective measures for the prevention and treatment of oral diseases. Research activities at the Dental Institute are directed toward this central goal, and considerable dimension has been added to both the intramural and extramural programs in recent years. The completion and occupancy of new dental laboratory facilities in Bethesda this year has permitted the long-awaited consolidation of resources under one roof and expansion of professional staff and investigative programs in both the clinical and basic science areas. In concert with progress in direct research has been the continuous provision of research grant support to expand and utilize the research activities of the Nation's universities, hospitals, laboratories, and other public and private institutions.

This notable progress has, at the same time, pointed up the need for more trained scientists to sustain and perpetuate gains already made. In this regard Congress has been particularly responsive to the need for more graduates to pursue careers in research and teaching. The fellowship and training programs, so vital to the furtherance of research productivity, now offer qualified and promising young people the opportunity of preparing themselves for full-time careers in dental research and for academic appointments as teacher-investigators. The training program has been in operation for 5 years. The direction the program has taken during this time has, of necessity, been dictated by the more immediate needs of dentistry; namely, a deficiency in the number of clinical and basic science teachers with training in research methodology. Encouraging progress has been made as evidenced by the fact that we now have 44 training programs at 38 dental schools and other institutions where some 200 individuals are being actively trained for careers in research and academic dentistry.

In another important area of training, we have now initiated programs in 42 of the 47 dental schools to provide instruction in the proper use of chairside assistants. This program is designed to increase the quality and quantity of dental services by the use of ancillary personnel with the long-range objective of relieving, in part, the growing disparity between the need for dental services and the ability to meet this need.

Within the last 2 years experimental research findings in the area of oral microbiology have shown that not only may dental caries be a very specific disease of bacterial origin, but scientists at the Institute have demonstrated its transmissible nature and established the specific causative agent in two different animal species. Although it would be premature to extrapolate these findings to humans at this time, the widespread circulation of this knowledge among both professional and the lay public promises to have a profound effect on the orientation of dentists, many of whom do not feel they are treating a disease when filling a tooth, and on the general attitude of a public that is not yet accustomed to consider tooth decay as a disease.

The current controversy over fluoridation continues today as a contradiction to an otherwise normal public viewpoint toward beneficial health practices. Seldom has there been a measure to protect the public's health which has been so effective, so certain, and so simple. Although the rate of expansion of this program has slowed in recent years, current Public Health Service figures on the increasing population served by controlled water systems are encouraging. These reveal that from 1951 to 1961 the number of fluoridated communities increased from 344 to 2,190 and the population served by these communities from 5 million to 42 million, or expressed in percent of the total population, from 3.3 to 23. In addition to the advantages of lower tooth decay rates in these communities, there is also a possible saving in manpower requirements in future years, which could actually amount to millions of saved dentist-hours.

In retrospect, fluoridation, backed by over a quarter century of research, has been available for over a decade, but the trend toward community acceptance has slackened rather than accelerated. This phenomenon of apparent disinterest in a proven health measure clearly invites further study to supplement our meager knowledge of socioeconomic factors that will influence the acceptance of other new research findings in the future. The serious implications of this problem were reflected in the special conference sponsored this year by the National Advisory Dental Research Council to develop methods for stimulating behavioral science research programs in the field of dentistry. From these discussions came specific recommendations to provide program support to selected dental schools for the addition of behavioral scientists to their faculties, and the extension of public health research programs concerned with sociological aspects of dentistry.

With this overview of new emerging needs in dentistry, encouraging progress has been made during the past year in both the intramural and extramural programs of the Dental Institute.

INTRAMURAL PROGRAM

The intramural program, now centered in the modern dental research laboratories on the grounds of the National Institutes of Health, consists of a cadre of scientists trained in many disciplines who seek to develop the knowledge required to understand the etiology and mechanisms of oral disease. With this new research facility, more adequate equipment and expansion of professional staff, has come the added responsibility to encourage and support collaborative activities with scientific groups beyond the Institute, and to further increase the dimension of our laboratory and clinical research at Bethesda.

Representative among broadly based studies now underway and programed for continued emphasis are: (1) research on cleft palate and other congenital anomalies involving growth and development of the oral and facial regions; (2) development of newer, recently advanced, concepts of dental caries etiology using the germfree animal technique; and (3) development of an increased emphasis on studies of periodontal disease including the relationship of general systemic factors to the disease; the casual significance of various microbic and enzymatic factors; the epidemiological patterns of the disease; and, the mechanisms of calculus formation and its relationship as a local factor to the disease process. The following discussion includes a selection of research highlights from these and related areas of the intramural program of the Institute.

Genetic studies

The association of certain hereditary factors with oral disease has been recognized for years. Yet the interrelated factors of genetic and environmental origin that contribute to cleft lip and palate, defective calcification, and susceptibility to dental caries and peridontal disease are still obscure.

To further the study of human genetics, and particularly its role in oral malformations and disease, the Council on Dental Research of the American Dental Association in cooperation with the National Institute of Dental Research conducted a special symposium in 1962 that brought together for the first time outstanding geneticists and dental investigators to exchange information on present and proposed studies. Indicative of the broadening base of dental research today was the presentation of papers covering recent developments in medical genetics, heritable diseases of dental interest, and genetic methods applicable to the study of intrinsic dental disorders. Recent research at NIDR in the field of human genetics has been concerned with clinical and laboratory studies of a newly described disease involving the faulty development of oral mucosa and with the further description of hereditary patterns in other conditions. Expansion of these programs in the coming year will include additional studies of the genetic mechanisms of known hereditary diseases and evaluation of methods for the diagnosis of those diseases having oral manifestations. Of particular interest to clinical investigators are the wealth of research opportunities to study hereditary diseases and anomalies among certain defined population groups in this country and abroad. In a foreign study completed this year deleterious effects of inbreeding among a large population were observed by a team of examiners comprised of geneticists, pediatricians, dentists, and anthropologists. While all data have not yet been evaluated there appears to be a death rate among offspring of first cousin marriages almost twice that found in a normal control group. Dental examinations also indicated a higher frequency of supernumerary teeth than is reported for Caucasians and an accelerated eruption of permanent teeth.

Dental caries studies

Studies using germfree animals continue to provide, as do no other experimental systems, a controlled approach to the testing of pathologic effects of oral bacteria and to the evaluation of constitutional and dietary factors in the disease process. The finding that dental caries can be caused in animals by a single strain of streptococcus has provided a firm base for plans to extend this activity.

Prenatal factors in oral disease

In studies of growth and development, congenital deformities such as cleft lip and palate have been induced by altering the supply of oxygen to rat fetuses and by altering the amniotic pressure during fetal development. In related studies, the influence of prenatal factors on dental decay was recently demonstrated with pregnant rats exposed to atmospheres high in carbon dioxide. It was found, for example, that females exposed early in gestation delivered young that were considerably more susceptible to dental decay than the offspring of unexposed control animals. Additional biochemical and morphological studies will seek a clearer understanding of this congenitally acquired susceptibility of dental tissues to attack.

Calcification

The process of mineralization within the body is of particular interest to dental and medical scientists. However, the underlying factors that regulate normal and pathologic calcification in certain tissues are still not clearly understood.

Basic studies of the crystalline component of dental enamel have been continued, with an eye toward defining more acurately the dimensions of the crystals and their orientation within the prismatic units of enamel. This work has been carried on mainly by electron microscopy and diffraction of mature and developing material, and it presently appears as if the crystals are considerably longer than previously thought. Determination of crystal arrangement, which is quite intricate, has been largely a matter of morphological definition. These studies designed to gain a clearer understanding of enamel crystallinity are essential for interpretation of the structural alterations involved in developmental tooth defects and caries.

A series of recent studies, involving the transplanting of tissues in the peritoneal cavity of rats, have shown that normally noncalcifying tissues, such as skin, will become calcified when implanted along with oral bacteria. Electron microscopy revealed striking similarities betwen the mineral deposits recovered from tissue transplants and those obtained from developing human oral calculus. Moreover, the finding that bacteria can induce the formation of hydroxyapatite in biological fluids suggests the possibility of immunological methods for the elimination of dental calculus, a main contributor to periodontal disease.

Periodontal disease

Studies of experimental infection with oral microorganisms related to periodontal disease were reported during the year. In these investigations, attention was focused on the possible role of bacterial endotoxins in the processes of periodontal disease. For example, endotoxins were isolated for the first time from all of the oral bacteria implicated in periodontal disease and specific histotoxic effects have been demonstrated in rabbits.

At the present time the formation of dental calculus in the gingival area is recognized as the most important immediate contributing factor to periodontal disease. Systematic studies of the bacterial deposits that initiate calculus deposition are, therefore, essential. Contrary to the general impression that filamentous forms predominate, completed studies show that various species of streptococcal bacteria outnumber all other types at all stages of calculus formation.

Another interesting development during the year was the preliminary observation that periodontal disease seems to arise in animals subjected to transfer of suitable tooth plaque material. The discovery of the infectious nature of plaque substance recovered from the periodontium may well lead to a profitable series of investigations on experimental periodontal disease. The mocrobial characteristics of these plaques are now under investigation and the possibility of inducing periodontal disease with pure cultures of organisms is being studied.

Epidemiological studies of oral disease

In the past, most studies in dental epidemiology have been concentrated upon caries which, in the United States, attacks early in life and can destroy the dentition before adulthood unless checked by preventive or treatment measures. In the United States today, tooth mortality from this cause has been reduced to a point where more teeth are actually being lost to the periodontal diseases than to caries, principally because of earlier and more adequate care of the teeth. In some other parts of the world, caries is very low in prevalence but periodontal disease is widespread and so severe that many young adults are virtually edentulous from this cause. Accordingly, periodontal disease studies have been emphasized in a program of international surveys carried out by the Interdepartmental Committee on Nutrition for National Defense.

During the current year, data from surveys in Lebanon, Trinidad, Burma, and with American Indians in Montana were added to material previously gathered by Dental Institute investigators in Alaska, Ethiopia, Ecuador, Chile, Colombia, South Vietnam, and Thailand. These studies have been analyzed as individual units and as components of a whole program, on the general hypothesis that populations depleted in any nutrient will show higher disease prevalences if such deficiency is etiologic for that disease. To date, wide differences in disease prevalence have been recorded; dental caries, for example, ranging from virtual absence in Ethiopia and parts of Alaska to rates as high or higher than those found in the continental United States. In contrast, few populations were found in which periodontal disease was not a major problem. These data are currently being evaluated to determine the role of nutrition in the causation of dental caries and periodontal disease.

Fluoride studies

The exact manner by which locally applied fluoride compounds confer protection to teeth is not completely understood. However, with the use of electron and X-ray diffraction techniques, scientists reported this year the isolation and identification of a substance that forms on the surface of teeth following exposure to stannous fluoride solutions. The increased acid resistance is due in large part to this protective layer identified as hydrous hydrated stannous oxide, which is very resistant to washing with water, etching and brushing with water alone, but readily damaged by brushing with an abrasive.

Scientists recently reported findings in a 12-year study of the efficacy of fluoride administered systematically in tablet form. They found that children who ingested a tablet containing 1 milligram of sodium fluoride every day for an average two-thirds of their lives compared favorably in caries protection with children of similar ages who drank fluoridated water. These findings suggest an alternate solution to those situations where, because of individual water supplies, such as wells, conventional fluoridation is not practical.

RESEARCH GRANTS

The Dental Institute has continued to encourage and support fundamental research in the various basic sciences of primary importance to clinical research in dental medicine. All of the 47 dental schools in the United States have now participated in the research grants program and during the year the number of active research grants totaled 455 at 133 institutions in 39 States and territories and 13 foreign countries. Approximately 80 percent of the funds allocated for research projects support research at these dental institutions. Fundamental studies in the field of dental research are aimed at reducing the degree of empiricism and establishing a more scientific basis for solutions to dental problems. The broad range of interests identified with research grants are indicated by the following four examples:

1. Prominent this year in the field of congenital anomalies was the award of a grant in support of a research program to explore a method of effecting dental-orthopedic adjustments of the premaxillary and maxillary elements in the infant with wide complete unilateral or bilateral clefts of the lip and palate. Early orthodontic adjustments, coupled with ideal palatal surgery and orthodontic guidance during the development periods, may aid materially in minimizing or perhaps eliminating one of the major problems of growth and development in this segment of the cleft palate population.
2. Noteworthy this year was the support of grantee studies using the germfree animal approach to the ecology of dental diseases. The merit of this program from an ecological standpoint is that it provides an approach to identifying important interactions of the oral flora and thus should lead to a better understanding of the forces governing establishment of the bacteria indigenous to the mouth. Also, if it should prove possible to establish the flora of man in rodents, an exceedingly useful tool for studying the role of the microorganisms indigenous to man would become available.
3. Another group of grantee investigators are investigating the nature and value of high-intensity sound in the amelioration of dental pain. They will attempt to determine whether the phenomenon is one of suggestion, distraction, or cross-sensory masking. Clinical subjects will be exposed to noise and different octave bands, concomitantly with stimulation with a tooth pulp tester, to determine the effect of the sound on pain. Rhythmic sound will also be used to compare its effect with that of meaningless noise. These studies may show that it is possible to attain by the use of sound a satisfactory temporary analgesia to replace the currently used drug methods.
4. A study is currently in progress to develop methods for the isolation of native collagen from dentin and peridontal tissue; to determine its chemical and physical properties; and to evaluate its ability to act as a substrate for bacterial collagenases and trypsin. The ultimate purpose of this study is to establish the collagen structure in dentin and periodontal membrane, and thereby clarify the role of collagen in resisting the stresses which tend to deform dentin and periodontal membrane. It is anticipated that much needed basic information about tooth structure and composition in relation to function will result from the study.

RESEARCH TRAINING

With the anticipated need for research oriented personnel, and with the establishment of new dental schools and expansion of others already in progress or planned, the requirement for individuals with training beyond the professional dental degree is expected to continue. Moreover, a trend toward more and lengthy clinical research continues to grow in university-affiliated dental schools, making this type of training at advanced levels increasingly necessary.

Our training programs, although still young, have shown encouraging progress. Funds awarded to date have permitted program directors to assemble qualified staffs and develop excellent training curriculums and experiences. The object here is to provide increased numbers of highly skilled individuals for careers in academic dentistry with particular emphasis on research qualifications. Additional attention is being given to the expansion of selected, currently operating programs in areas that need special emphasis, such as cleft palate, periodontal disease, epidemiology, and the behavioral sciences as related to the sociological aspects of dentistry.

The dental student training grants program modestly begun last year in 42 of the 47 dental schools has progressed well. This program is shown in our budget but is administered by the Division of Dental Public Health and Resources. Briefly, this program of grants to dental schools is used to instruct dental students in the proper use of chairside assistants in order to increase the individual productivity of the student-dentists who eventually will provide a greater amount of good dental care to the public. It is intended that increased utilization of auxiliary personnel will significantly extend the services of the dental profession and thereby help relieve the growing shortage of dentists.

Fellowships

The primary efforts of the research fellowship program are directed toward graduate training in the basic sciences. Active support of qualified applicants for predoctoral, postdoctoral, and special fellowships will continue in 1963 as a vital part of the overall developmental program for dental research and teaching.

In the coming year emphasis will continue toward support for advanced training in the behavioral sciences related to dentistry, cleft palate, periodontal disease, basic areas related to dental caries, and other oral disorders. In the past the dental student part-time fellowship program has been instrumental in interesting young men in dental research. This program will be continued by the schools through the new NIH-administered general research support grants.

In conclusion, Mr. Chairman, the request for the National Institute of Dental Research in 1963 is $17,199,000. This allowance for 1963 will provide increases of: (1) $1,687,000 to support approximately 40 new research projects and broadly based program activities; (2) $134,000 for direct research; (3) $51,000 for review and approval of grants; and (4) $23,000 for administration. The request for 1963 is distributed among program activities as follows:

Grants:	
Research	$9,123,000
Fellowships	882,000
Training	3,741,000
Subtotal, grants	13,746,000
Direct operations:	
Research	2,858,000
Review and approval of grants	424,000
Administration	171,000
Subtotal, direct operations	3,453,000
Total, 1963 appropriation request	17,199,000

DENTAL CARIES

Mr. Fogarty. You said in your prepared statement that dental caries may be caused by bacteria?

Dr. Kreshover. Yes, sir.

Mr. Fogarty. Whatever happened to the study that was made a few years ago in Chicago in cooperation with the Lobund Laboratory at Notre Dame on germ-free animals? I though that related to this same problem.

Dr. Kreshover. It did, sir. I would like to comment on this if I may.

Mr. Fogarty. Go ahead.

Dr. Kreshover. In short, there are two historical events in the background of information, or leading to the present information, that today recognizes dental caries as a transmissible and infectious disease.

These two important events were, one, the study you referred to at the University of Chicago, in cooperation with the laboratory of bacteriology at Notre Dame, in which the germ-free tank was used to explore the possibility of developing dental caries with dietary additives alone; dietary additives which have been recognized for many years in the conventional animal to cause dental caries.

Mr. Fogarty. What do you mean by "dietary additives"?

Dr. Kreshover. In the conventional animal, or in man, a diet high in refined sugars, in reduced sugars, such as sucrose and glucose, will frequently relate to an initiation of dental caries.

Mr. Fogarty. What about so-called soft drinks.

Dr. Kreshover. Presumably this also has been related in many instances to a high incidence of dental caries in some of the few studies that were done.

Mr. Fogarty. Is there much difference between them?

Dr. Kreshover. I doubt it very much.

These are high sugar content drinks and unquestionably they can relate to dental caries incidence.

I was on the germ-free experiments at Notre Dame in collaboration with the University of Chicago. Animals—rats for example—in a normal environment and with the proper diet would develop caries. However, animals introduced at the time of birth, of course, into a germ-free environment so that they are bacteria free, would not develop caries under any other experimental conditions that were introduced.

About the same time that the Lobund experiment demonstrated the essential feature of bacteria as a causative agent in dental caries, Dr. McClure, of our Institute, operating in our intramural program, subjected rats to penicillin, which was administered over a given period of time. The action of the penicillin in destroying the oral microflora; that is, the bacteria which ordinarily had been related to dental caries, also demonstrated their essential role in the causation of dental caries.

STREPTOCOCCUS RELATIONSHIP TO CARIES

This was one important step and it was followed shortly afterwards by one of our other intramural scientists, Dr. Keyes who, quite by chance but with the wonderful imagination and inquisitiveness of a scientist, was able, following the mistake of introducing a caries-immune animal previously thought to be immune because of heredity, into another cage that contained caries-active animals, found that the previously immune animal developed caries. He was observant enough to recognize that this was an unusual event and possibly demonstrated some transmissibility characteristic.

Therefore, he repeated the experiment and confirmed it. This was followed by Dr. Fitzgerald, one of our other scientists in microbiology, who in the period of the last 2 or 3 years, has been able to demonstrate the caries relationship of the streptococcus in the hamster. When these animals were inoculated they could pass the infection on to other animals contained in the same cage, or one could take an inoculum from the caries region of one animal and introduce it into a previously noncaries animal and demonstrate caries activity.

Mr. Fogarty. You mean to say if we could find something that would eliminate streptococcus, it would help in dental caries, also?

Dr. Kreshover. The thing we guard against very carefully is any premature application of these findings in the laboratory animal to man. The next obvious step that we are going to emphasize, of course, is to test this hypothesis in man. We have clinical studies now planned for the future where we hope we might be able to identify either a specific organism or a specific group of organisms that can be related to dental caries in man. We are in the process of doing this.

CLEFT PALATE

Mr. Fogarty. What about cleft palate? We discussed this at some length with Dr. Galagan. I made the statement then that we had been doing a lot of talking about this problem for at least 10 years, but we have never carried on a real good program in this area. I for one think that we ought to be doing more than we are doing. Do you want to talk on that and tell us what the problems are and what you think we can do that is not covered in your budget?

Dr. Kreshover. We quite agree, Mr. Chairman, that we have a major problem to deal with in the field of this disability of cleft palate and cleft lip, but I believe we are making fine progress, although we still do not have an answer.

Mr. Fogarty. You do not have any photographs of before and after treatment, do you?

Dr. Kreshover. Yes, sir; we do. I do not have them with me.

Mr. Fogarty. Could you send some to the committee illustrating what can be accomplished?

Dr. Kreshover. I would be very happy to do this.

I believe in short, Mr. Fogarty, the two essential problems that we face in the cleft palate field are, No. 1, clarification, a better understanding of the cause of these abnormalities, and No 2——

Mr. Fogarty. Whose responsibility would that be? Would that be some other Institute?

Dr. Kreshover. I believe any scientist's responsibility.

Mr. Fogarty. Would this be in connection with the Dental Institute?

Dr. Kreshover. Yes, sir. We are engaged in this type of research. The difficulties that have been faced in recent years to better understand the cause of cleft palate have to do with a swing of the pendulum, if you will, between those who go completely overboard in attributing the difficulty to genetic disturbances or abnormalities, and on the other side of the fence those who go completely overboard in attributing it to local or environmental factors. The truth of the matter probably is that it is a combination of the two, and that we cannot identify in man a situation of cleft palate and just arbitrarily say, "This is due to heredity," nor can we look at a situation and say, "This is due to environment." It unquestionably is a combination of the two.

Mr. Fogarty. You say unquestionably it is?

Dr. Kreshover. Yes, sir. This is a generalization, of course.

Mr. Fogarty. If you know that now to be a fact, why don't we find out the cause, then?

Dr. Kreshover. I am saying this is a generalization. I am quite equally certain that there are situations where we can demonstrate a hereditary pattern where the cleft palate defect is passed down from generation to generation.

Mr. Fogarty. Do you have any thoughts in mind about what you could do if you were given a certain sum of money to just work in this area?

Dr. Kreshover. I believe we are doing a fine job as we stand right now. This is not to argue against the matter of money.

Mr. Fogarty. You are not even scratching the surface?

Dr. Kreshover. Yes; I believe we are, very much so.

Mr. Fogarty. You have not made much headway in the last 10 years. If you have, this committee has not been informed of it.

Dr. Kreshover. I would like to tell you then a little bit about what I think is headway.

CAUSES OF CLEFT PALATE

Mr. Fogarty. Tell us how close you are to finding out the cause or how close you think you are.

Dr. Kreshover. No. 1, in family studies as well as in animal studies of carefully selected genetic strains, it is possible to demonstrate a clear-cut hereditary pattern of where a cleft palate can be passed on from generation to generation. This is the pure genetic component.

On the other hand, in other experimental animal studies we are able to demonstrate, with certain chemicals and other factors that can be introduced in an environmental sense, that we can produce cleft palate quite specifically in practically 100 percent of experimental cases.

This can be done by the administration of cortisone, as an example, to the animal—this, of course, has to be in the intrauterine or the prebirth state; we can create cleft palate by interfering with the local conditions of the fetus in the uterus in a certain period of time by, for example, puncturing the amniotic wall. You get an expression of some amniotic fluid and because of this you get a compression of the amniotic membranes on the fetus. This is theory. We feel it is true. With the compression of the amniotic membranes on the fetus, you have a compression of the head of the fetus in the fetal position against the thorax, and with this compression you have thrust or pressure of the tongue to the roof of the mouth. At this period of the development of the rat fetus, the palate is not yet closed and with the tongue in the roof of the mouth, you interfere with the normal closure of the two palatine shelves and they cannot come together. This is a beautiful demonstration, I think, of a local factor that can cause cleft palate.

We have made, I think, considerable headway in the experimental animal. We are in the process of making, I think, good headway in man by the application of many of these findings in the experimental animal to man.

Mr. Fogarty. What kind of research program do you have going on now?

TREATMENT OF CLEFT PALATE

Dr. Kreshover. I would say, Mr. Fogarty, that most of the experimental approach that I have made reference to has been pursued in our Institute as part of our intramural program, as well as in a few outside universities. These are rather few in number. On the other hand, in many of our institutions we are making a very favorable advance in the second aspect related to the treatment of cleft palate, the aspect you referred to before in terms of "before and after."

I can refer to places like the Lancaster Cleft Palate Clinic in Lancaster, Pa., which is doing a fine job; I can refer to the University of Iowa, which is doing an excellent job also.

Mr. FOGARTY. Are they on their own or have they received Federal grants?

Dr. KRESHOVER. This is on grant support in these institutions.

Mr. FOGARTY. In both cases?

Dr. KRESHOVER. Yes, sir.

Mr. FOGARTY. How much is Iowa getting?

Dr. KRESHOVER. I do not know.

Mr. FOGARTY. Will you supply that for the record?

Dr. KRESHOVER. Yes, sir.

(The information requested follows:)

In 1962 the University of Iowa received $76,970 for cleft palate research.

POSSIBILITY OF MORE EFFECTIVE PROGRAM

Mr. FOGARTY. The reason I am asking these questions, I am trying to develop something here where we might be able to help you. I do not think you are doing enough. You think you are, but I do not think you are.

Let me give you an example. A few years ago when Dr. Bailey was head of our Neurological Institute, we were able to get him to say, under a little bit of pressure, that if he had more funds they might be able to find out what causes prematurely born children to go blind soon after birth and because of the committee's knowledge of Dr. Bailey's background, and having some confidence in his suggestion, we appropriated more funds, and within a year they had the answer.

Maybe that was a lucky strike. We now also have activity in the same Institute in Puerto Rico, another experiment going on with monkeys in the area of mental retardation. We are supporting it with the hope that we may find some clues.

Do you have anything in mind that if you had the resources you could put on some sort of—I do not like to use the term "crash" but I do not know what other term to use—a crash program for a year or two to get more accomplished in this area than we are doing now. This takes you out from under any instructions that you might have received from anybody so you can tell us what you think now.

Dr. KRESHOVER. My instructions were only to do a good job.

Mr. FOGARTY. There will be some members from the American Dental Association here in 3 or 4 weeks. We will probably ask them the same thing.

NEED FOR A BROADER RESEARCH BASE

Dr. SHANNON. I would like to talk to one aspect of this while Dr. Kreshover collects his thoughts. I would say, first, that the problem of cleft palate is a very complex problem and is representative of a series of general problems that relate to congenital defects. In each case when one inquires into the generalities of causation one finds that there are combinations of genetic and environmental factors.

In the development of the overall programs at the NIH over the past 15 years, primary emphasis was given during the initial 10 years to those important chronic illnesses that had very high mortality rates. During the past 5 or 6 years it has been possible to broaden the programs with the funds being made available to encompass some of the equally important programs relating to problems of disability rather than problems of death. For example, we have common communicable diseases, such as the common cold and the like, that do not cause death but do cause disability.

Mr. FOGARTY. We have been spending a lot more money on the common cold than we have on cleft palate.

Dr. SHANNON. Yes, sir. I would point out that about 5 years ago general programs in genetics and programs in human genetics were launched for the first time. Programs in what is called comparative morphology, comparative development of organs in animals other than man, chemical embryology; effect of chemicals in specific organ development have just begun to receive systematic attention, both in training and research. I would say that Dr. Kreshover's problem is probably not going to be answered in a definitive fashion by simple attention to cleft palate as such, but rather by broad support for genetics, human genetics, comparative morphology.

The thing that Dr. Kreshover requires as a base for work on cleft palate is a much broader underpinning in the less differentiated studies. If he were asked, I think he would agree that to develop a program for cleft palate as such the basic underpinning would have to be pretty much the same as the program that is being developed for congenital heart disease, for some of the congenital brain diseases, and the like. I agree with you, Mr. Chairman, that there is not enough being done.

Mr. FOGARTY. This sounds good, but sometimes unless you pick out something specific that the general public and laymen in Congress can understand as a real problem, this research support gets lost in the shuffle. I have been listening to this problem of cleft palate now for 10 or 12 years. I just think that more should have been done in the past, and that more can be done in the future than is being done now.

Dr. SHANNON. Mr. Chairman, I agree that more could be done now, but if this is going to be profitable it has to be done all up and down the line, including and requiring first a substantial broadening of the base on which the applied studies are built.

Mr. FOGARTY. All right. Go ahead, Doctor. Now what do you think?

Dr. KRESHOVER. I would certainly concur in the remarks of Dr. Shannon.

RELATIONSHIP TO RESEARCH ON OTHER DEFECTS

I think a demonstration and illustration of this is in our own cleft-palate research, where we have not only been able to demonstrate by the application of certain factors, chemical and otherwise, the initiation of cleft palate but also of clubfoot and of defects of the cranium and of abnormalities in terms of closure of other of the visceral structures, and organs. By closure, I mean completed development, so that it is a broad-base problem. I do not think we are going to get to the bottom of the cleft-palate story until we also concurrently get to the bottom of the development of other anomalies.

The whole thing is not possible to divorce or fragment in terms of research approach.

I believe as far as the dental program is concerned our principal interest in developmental anomalies—the effect on the mouth, face, and related structures—can be boiled down also to other related problems which I think are inescapable and they relate to dollars as they might ultimately relate to facilities; for example, where are all of these programs going to be mounted? I think these other issues are important, also.

I would feel that under the circumstances of where we stand today, we are making very rapid headway and I think most of our headway has just been in the course of the last 2 or 3 years. I think we are going to continue to make strides in the future.

POTENTIAL FOR DIRECT CLEFT PALATE RESEARCH

Mr. FOGARTY. But if I were to ask Dr. Nagle or someone in his capacity about the same question, he would say, "Positively. We have facilities and manpower that we could use in this area."

Dr. KRESHOVER. At New York University?

Mr. FOGARTY. Yes.

Dr. KRESHOVER. I am sure this is so.

Mr. FOGARTY. I'm sure there are others. I just picked his name because he has been before the committee on previous occasions.

I would guess he would say, "We could spend a lot more money in this area and we have the manpower and facilities available."

Dr. KRESHOVER. New York University, Mr. Fogarty, as you may know, has recently initiated a program in cleft palate research which is a type of program grant that you have heard a lot about. I think they are beginning to do a fine job.

Mr. FOGARTY. But as far as you are concerned, you think you have gone as far and as fast as you can now?

Dr. KRESHOVER. No. I could never say that. I believe we are making fine progress. It would be very difficult to say what specific dollars might do in terms of the future course of events.

Mr. FOGARTY. About what do you think a stepped-up program would cost?

Dr. KRESHOVER. In cleft palate alone, Mr. Fogarty?

Mr. FOGARTY. What else would you take into an overall study along with cleft palate?

Dr. KRESHOVER. I would refer in addition to the problem of cleft palate and an accentuation of effort there; that we need a comparable effort in the field of periodontal disease, in the field of restorative dentistry as it relates to the development of new materials for filling of teeth which we do not have an adequate answer to today—adhesive properties of materials. This would bring in the recruitment of polymer chemists, for example, in this and in other areas.

Mr. FOGARTY. I think they are all necessary, too, but from my experience if we pick out one phase of these problems we are able to get more action than in a general approach. It seems to me that the problem of cleft palate is one of the worst.

Dr. KRESHOVER. It certainly is.

COST OF STEPPED-UP RESEARCH PROGRAM

Mr. FOGARTY. Supply for the record what you think could be done in this area if you had more funds and how much would be required to carry out a reasonable program to make a real attack on this problem.

Dr. KRESHOVER. I would be very happy to.

Mr. FOGARTY. In view of the facilities and manpower available, not only in your own Department but throughout the country.

(The information requested follows:)

CLEFT PALATE PROGRAM

While defective genetic composition is of unquestioned importance in the etiology of cleft palate and harelip, it has become increasingly apparent that alterations in the intrauterine environment can significantly affect the embryonic development of the mouth and related structures. Studies supported by the National Institute of Dental Research have shown that not only may a single type of injurious agent cause different types of developmental anomaly, but that a specific type of malformation may be caused by a wide variety of environmental factors. Ample evidence now exists that the period of pregnancy during which an injurious agent is present may well determine the nature of the deformity. For example, in high dosage X-ray irradiation to the fetus, different types of abnormalities can be induced depending upon which organ systems or tissues are undergoing development at the time of exposure. Similarly, a number of different types of injurious factors such as oxygen deprivation, nutritional deficiency, and endocrine change, can cause varied types of malformation including cleft palate and harelip. Thus while the overall problem of oral and facial abnormalities of development is extremely complex, research contributions, to date, permit certain generalizations to be made. Principal among these are that the incidence and type of developmental deformity produced will vary with the nature of the injurious agent, its dosage, the stage of pregnancy when applied, and the genetic constitution of the affected animal or human.

Other aspects of the cleft palate problem relate to the broad and important question of treatment methods and the recognition of the large diversity of professional interests involved which include oral and maxillofacial surgery, orthodontia, prosthodontia, speech pathology and therapy, otolaryngology, psychology, and genetics.

In order to continue an expanding and increasingly productive program in the many aspects of the cleft palate problem, emphasis should be given to the support of broad program projects of fundamental research, to clinical investigations of treatment procedures, and to studies concerned with the evaluation of the influences of maternal health on fetal development. Essential for the fruitful conduct of these varied research activities are the provision of adequate research facilities and a qualified resource of scientific manpower.

While it is important to recognize that the cleft palate problem, from the standpoint of etiology and eventual prevention, cannot be divorced from the total broad field of congenital defects, a major share of the repsonsibility must be borne by dental research. Thus, the professional judgment budget of the Dental Institute for 1963 has planned for the establishment of two multidisciplinary programs, over those allowed in the President's budget, in several of the more outstanding biomedical-dental centers in the country, and for supplemental grants to further expand existing programs in cleft palate research. This would cost between $200,000 and $250,000. Additional provisions in the professional judgment budget were made to apply approximately $75,000 to $125,000 of fellowship and $150,000 to $250,000 of training money to the support of graduate educational opportunities in the basic biological and clinical fields of research. These would be directed toward such scientific disciplines as developmental biology, neurophysiology, speech physiology and pathology, and other fields vital to the furtherance of the cleft palate program. In direct research operations, $82,000 was applied in the professional judgment budget to the support of expanded activities related to the genetic and epidemiological aspects of the cleft palate problem.

CHAIR-SIDE ASSISTANTS

Mr. **Fogarty**. You mentioned chair-side assistants. What is your definition of a chair-side assistant and a hygienist? What is the difference between the two?

WOONSOCKET PROGRAM

Dr. **Kreshover**. I was waiting for this type of question because I realize or recognize as you do that the first major demonstration of the usefulness of the chair-side assistant was in your home city of Woonsocket in 1953.

Mr. **Fogarty**. That is not my home city, but it is in Rhode Island.

Dr. **Kreshover**. That is right. They demonstrated as early as this that by utilizing hygienists or other qualified people at chair-side to perform such seemingly simple operations as anticipating, as the assistant or the chief nurse in the operating room anticipates the needs of the surgeon, anticipating the needs of the dental operator and handing him the necessary instruments, assisting him in the preparation of filling materials for insertion in teeth, and otherwise furnishing him with an additional two hands that are highly skilled, that he is able to cut down on his patient time approximately one-half; this would mean, of course, that he would be able, just to point to a general example, to see perhaps twice as many patients in the course of a day as he would ordinarily.

Mr. **Fogarty**. As I remember this program it was about a 5-year program.

Dr. **Kreshover**. No, sir. The chairside assistant may be trained very adequately in the course of about a year.

Mr. **Fogarty**. I refer to the program in Rhode Island. It lasted 4 or 5 years?

Dr. **Kreshover**. Yes, sir.

Mr. **Fogarty**. It was mostly among schoolchildren?

Dr. **Kreshover**. Yes. There were about 6,000 schoolchildren included in the study and the principal objective of the study was to evaluate accumulated dental needs on the one hand and the maintenance needs on a yearly basis on the other.

Mr. **Fogarty**. I know it surprised everybody.

They were surprised to learn the need that existed and the lack of care being given these children.

Dr. **Kreshover**. Yes, sir.

Mr. **Fogarty**. Will you supply for the record the report on that study or a summary of the report.

Dr. **Kreshover**. Yes, sir, a reprint or a summary of it.

(The information requested follows:)

Woonsocket Program

The Woonsocket, R.I., dental service program was a joint undertaking by the city of Woonsocket, the Rhode Island State Department of Health and the Public Health Service designed to demonstrate how the problems of accumulated and maintenance dental care needs could be met in a relatively large population of children.

During the course of the study, dental examinations and complete dental treatment were given to approximately 6,000 children ranging in age from 5 to 16 years. Every child received at least one prophylaxis and more than 5,000 received topical fluoride treatments. Because of the substantial backlog of accumulated dental needs among the children, it was necessary to operate the program for approximately 6 years before a maintenance status of dental care was achieved.

Results of the study clearly demonstrated that if dental services are provided on an annual increment basis, the average dentist can provide to at least three times as many children with the same expenditure of professional chair time. The study also provided an important assessment of the effective use of dental assistants in reducing the dentist man-hours required for the treatment of patients.

In retrospect, the Woonsocket and other similar studies such as that in Richmond, Ind., provided a clearer definition of the role of the chairside assistant in rendering dental treatment. Moreover, the valuable information gained is now contributing importantly to the design of chairside assistant programs being established under Public Health Service training grant support in our dental schools. Such progress is perhaps best appreciated when viewed in light of the expanding population and the declining ratio of dentists to population.

FOLLOWUP OF PROGRAM

Mr. Fogarty. In that area this program did a lot of good for the children. What happens after the program is completed?

Dr. Kreshover. I think probably two things happen: No. 1, you have gained tremendously in terms of knowledge, just like an experiment in the laboratory that has been completed. You have learned from it, even though it has been completed; secondly, I think you also educate others at the scene to the importance of what has been demonstrated. I think this has been very well demonstrated for all of our cities throughout the country.

Mr. Fogarty. Has any followup study been made?

Dr. Kreshover. I think the followup is best demonstrated by the extremely vigorous activity of the Rhode Island Society of Dentistry for Children. I believe you met with this group not too long ago. I think the application of what was learned in this study in Woonsocket to all practitioners of dentistry, not only the pedodontists concerned with children but the general practitioner, has been paying tremendous dividends since that time, not only in Rhode Island, but other States as well.

Mr. Fogarty. I was astonished at the number of children who needed care and were not getting it at the time and the good work that was performed under this project. Now I am wondering whether that has been followed through—whether these children are getting better dental care now than they were 10 years ago.

Dr. Kreshover. I am sure, Mr. Fogarty, that they are. I believe one of the other important advances that has taken place in the problem of dentistry for children is reflected in the observations made at the Guggenheim Clinic in New York, where they see approximately 9,000 children a year. They recognized that about 50 percent of the dental caries problems begin at the age of 2, so I think we have more learning to do in terms of our treatment of children and our concern for children. It is not a problem that begins at the age of 6 but at 2.

ACCEPTANCE OF CHAIRSIDE ASSISTANTS

Mr. Fogarty. I recall that was developed at this Rhode Island study. Some dentists are not yet convinced that a chairside assistant is a good thing, are they?

Dr. Kreshover. Although I have yet to meet one that is not aware of its importance, I believe it is a matter of education and training.

Mr. Fogarty. I was under the impression there are many dentists who never have used one and perhaps never will.

Dr. Kreshover. I was reminded by Dr. Shannon of an important point here, and he has been interested in this program, as you know—that is, the dental practitioner and the medical practitioner, faced with something new, will take a reasonable period of time before he becomes convinced of it.

Mr. Fogarty. I think the American Dental Association recognizes that, too.

Dr. Kreshover. I think so.

Dr. Shannon. The use of the assistant is very widespread now.

Mr. Fogarty. They recommend it, I know. They tell me some dentists are still not sold on it so they have a job yet to do in educating them.

Dr. Kreshover. Yes.

FOLLOWUP OF WOONSOCKET CHAIRSIDE ASSISTANT PROJECT

Mr. Fogarty. I know of no study made to follow up the Rhode Island demonstration project in order to determine whether this care has been continued and in order to determine whether the dentists in this section of Rhode Island have more chairside assistants than the average in other similar cities of the country.

Dr. Kreshover. To the best of my knowledge there has not been a followup, Mr. Fogarty.

Mr. Fogarty. Wouldn't that be useful?

Dr. Kreshover. I shall see that this is discussed. I think it might be a good idea.

DENTAL HYGIENISTS

Mr. Fogarty. Go ahead and tell us about the hygienists.

Dr. Kreshover. The hygienist is a young lady who receives a 2-year educational experience.

Mr. Fogarty. Is there any reason it has to be a lady?

Dr. Kreshover. This is an interesting question and it has an interesting answer. I think most States by law require that it be a lady.

Mr. Fogarty. Why is that?

Dr. Kreshover. I don't know. There has been fine experience in terms of some of the Scandinavian countries where many women take up the profession of dentistry, to the degree of perhaps 75 percent. Perhaps this is a carryover in terms of some of our experience.

Mr. Fogarty. Dr. Scheele's wife was a dentist, was she not?

Dr. Shannon. She is. Dr. Scheele's wife takes some time off each year, goes back to her home town, and practices for a number of weeks to maintain her skill.

Mr. Fogarty. Go ahead.

Dr. Kreshover. The dental hygienist has an educational experience of 2 years. At the last count I believe there were some 34 schools for hygienists in the United States, and there are in the neighborhood of about 4,000 dental hygienists practicing full time. These skilled people, Mr. Chairman, function in dental offices and pursue certain independent activities without supervision.

These include such things as what is called a prophylaxis; that is, removal of stain and other material from the teeth, which is still an important job if you are to successfully tackle the larger problem of periodontal disease.

The dental hygienist also serves in many dental offices in many assisting capacities.

The dental assistant, on the other hand, is a person who does not have the duration of educational training that the hygienist does. This person would be more analogous, perhaps, to a subprofessional individual in supporting the role of the dentist at chairside, helping him mix filling materials, and so on.

TRAINING ASSISTANTS AND HYGIENISTS

Mr. Fogarty. What about the number of chairside assistants and hygienists? Is the number going up or has it gone down? Do you have sufficient teaching facilities to take care of all applicants?

Dr. Kreshover. This is a new program, Mr. Fogarty. I believe the experience today in training chairside assistants is one which would demonstrate perhaps adequate facilities. In the chairside assistants program in the existing 42 dental schools where the program is in operation, I believe there are 7 more to go if we are to do it in all 49 dental schools—the experience is one where the dental assistant works with the dental student so that there probably would not be any failing on the part of facilities for bringing these people into a fine condition of training today.

COMMITTEE ON NUTRITION FOR NATIONAL DEFENSE

Mr. Fogarty. You mentioned in your prepared statement that Dr. Daft might have something to offer later.

Dr. Kreshover. I referred to the program of the Interdepartmental Committee on Nutrition for National Defense, more simply referred to as the ICNND.

For some few years now we have been extremely interested in their activities. There was recently an Assistant Director appointed to assume increasing responsibility for this important operation. The Assistant Director is within the organization of the National Institute of Arthritis and Metabolic Diseases.

Our role in these activities has been one of furnishing ICNND with a dental officer to accompany their nutrition survey teams as they take part in the studies in countries which invite their participation.

To date we have completed such studies in a number of foreign countries, and I believe we have made very important strides in terms of very valuable information on the relationship of nutritional factors to such conditions as dental caries and periodontal disease.

I would like to point out some examples. Quite recently two of the studies——

PERIODONTAL DISEASE

Mr. Fogarty. Before you start, terms such as "environmental" health do not mean much to the general public, and the term "periodontal disease" doesn't mean much either.

I know it is a serious problem but the term "periodontal disease" to the average layman does not disturb him, in fact, he doesn't even know what you are talking about.

Dr. Kreshover. Periodontal disease is one of the principal causes of loss of teeth in adult life. It has been conservatively estimated that at age 65 probably all people have periodontal disease. It is extremely prevalent. It has clinical manifestations characterized by inflamation. The inflamatory part will involve not only the tissues surrounding the teeth themselves but also extend to involve the supporting bone, the so-called alveolar bone. This bone is involved by an inflamatory process that will——

Mr. Fogarty. I want it in words that I can remember and use, words which have some meaning to the average layman.

Dr. Kreshover. The disagreeable word is called pyorrhea.

I can do this by pointing out that each tooth in the mouth, and there are 32 teeth in the adult individual, is contained in its socket, so-called, by an attachment of tissue. This attachment is called an attachment apparatus. Because of disease, and the disease cause is unknown except we know it is an inflamatory process in most instances, there is a destruction of this attachment tissue, and if the attachment tissue is destroyed the tooth obviously will not be retained in its socket and ultimately it would become loosened and lost.

Mr. Fogarty. That does not kill a person, does it?

Dr. Kreshover. Neither does the common cold but it can be extremely severe.

SERIOUSNESS OF PERIODONTAL DISEASE

Mr. Fogarty. Tell us how severe it is.

Dr. Kreshover. The mouth is the portal for all of the food that we ingest. It has to be masticated. If the teeth are lost and not adequately replaced we obviously can end up with a nutritional problem.

Similarly, in the process of pyorrhea, so-called, or periodontal disease, there can be an occurrence of infection locally, which there frequently is. Because of this, and of other situations reported in the literature which are not uncommon, the development of a bone injury in an extremity, for example, can oftentimes cause a localization of organisms at that site of local bone injury. This occurs as a result of the organisms from the diseased oral tissues sometimes finding their way into the circulating blood, which is the bacteremia, and following an injury to some distant site it is extremely possible——

Mr. Fogarty. Give us an example.

Dr. Kreshover. Osteomyelitis is one example. Another example is——

Mr. Fogarty. How does it bring that about?

Dr. Kreshover. Bacterial carditis is perhaps one of the most important examples. This is where a child, for example, or an adult, would have a diseased heart. The bacterial——

Dr. Terry. This refers to an infection usually on the heart valves. The thing that happens here is that ordinarily a person who does not have a damaged heart or a scarred valve in a heart, would probably not have great difficulty if there is a release of bacteria into the bloodstream. On the other hand, where the person earlier has had some damage to his heart and has had some scarring of the valves, then when bacteria get into the bloodstream they tend to localize and to set up actual infections within the heart valve. This is one of the very serious problems we have had in the past.

The use of antibiotics and other measures recently have tended not only to bring it under control in terms of preventing it but also in terms of curing cases which actually occurred.

It is an example of where bacteria that get into the bloodstream may localize on a particular organ or a particular place in the body and set up an infection and result in the death of the individual.

Mr. FOGARTY. All right, those are two good examples. Please continue.

Dr. KRESHOVER. I was referring to the importance of the ICNND collaborative studies as related to our Dental Institute and pointing up some of the examples where we have made profitable advances.

In South Vietnam, for example, and in Thailand more recently, some of the observations have demonstrated what seems to be a nutritional component, particularly in the area of periodontal disease, where there is a seeming relationship, which has to be checked out, between a vitamin A deficiency and an extremely high incidence of periodontal disease in both of these countries.

NEED FOR CALCIUM FOR PROPER DENTAL DEVELOPMENT

Mr. FOGARTY. What about the use of milk? Is milk good for teeth? I was always told if I drank a lot of milk I might have better teeth.

Dr. KRESHOVER. It is an interesting thing that in the development of the skeletal system of man the intake of calcium, as an example, will first be applied to the developing bones and to the teeth as well.

I should point out that in a calcium deficiency the teeth will not lose calcium whereas the bones may lose calcium.

The point I am trying to make is that in the development process, in the building up of skeletal tissue and teeth, obviously adequate levels of calcium and other minerals are essential.

Once the teeth are completely formed a deficiency in these mineral components will not have an effect, so far as we know, on the dental tissue.

There is a question which also would be important to comment on which has to do with the relationship of calcium to pregnancy and the possibility of how this might relate to tooth loss.

We cannot say very much about this because it is one of the traditional beliefs, which has not been too adequately substantiated, that during pregnancy there is an unusually high incidence of dental caries activity and subsequent tooth loss.

To get back to my previous comment that once the tooth is completely formed there is not a following deficiency in terms of calcium loss, there have been many attempts at trying to track down why in pregnancy you have a high incidence of dental caries, if indeed you do. I don't know that this has been checked out.

Some people point out that during pregnancy the expectant mother would be less apt to want to get out and visit a dentist and consequently neglect might be one of the important issues.

BUDGET PROPOSAL 1963

Mr. Fogarty. Your appropriation for 1962 is $17,340,000. The request for 1963 is $17,199,000.

Dr. Kreshover. Correct, sir.

Mr. Fogarty. That is not progress. You are going backward. This looks like another example of not even getting back the reserve in 1963 which was applied to you in 1962.

Dr. Kreshover. Measured in terms of achievements we have made, and referring again to some of the important points you brought out in questioning of this witness, I believe we can demonstrate appreciable degree of progress, Mr. Chairman.

Mr. Fogarty. You are on the opposite side of the table and I suppose you have to do the best you can. If you received $2 to $3 million more do you think it could be put to good use?

Dr. Kreshover. Yes, sir.

Mr. Fogarty. And it can be used efficiently and to the best interest of the people?

Dr. Kreshover. Yes, sir.

APPLICATION OF RESERVES

Mr. Fogarty. Your reserve is $2,031,000. All but $321,000 is forced savings.

Dr. Kreshover. Yes, sir.

Mr. Fogarty. How is this reduction for forced savings being applied?

Mr. Seggel. $316,000 in research grants, $238,000 in fellowships, $1,050,000 in training, and $106,000 of direct operations.

FUNDS FOR TRAINING PROGRAMS

Mr. Fogarty. Do you have requests for funds for good training programs which you canot finance?

Dr. Kreshover. Yes, sir.

Mr. Fogarty. Is there still a shortage of trained people in this field?

Dr. Kreshover. Yes, sir.

Mr. Fogarty. Is there unused potential for training which could be used if funds were available?

Dr. Kreshover. Yes, sir.

Mr. Fogarty. I think I am more right than you are when I said this is not a good budget which is being presented here. You say you have all of these shortages, especially in the training field, and you ask for less in 1963 than you have in 1962.

BUDGET FOR 1963

The only increase of any consequence over what you are being allowed by the Secretary to spend this year is $1,687,000 for research grants.

Mr. Seggel. That is right.

Mr. Fogarty. You have no increase for fellowships and no increase for training.

Mr. Seggel. That is right.

Mr. Fogarty. It is also brought to my attention that for 1963 this budget will be over $500,000 short of being sufficient to finance estimated approved research grant applications.

Dr. Kreshover. In 1963; yes.

Mr. Fogarty. That is not good for dentistry, and the training program in this field of dentistry is important. We have discussed this with Dr Shannon, Dr. Terry, and others. This is one of the newer Institutes. I believe this is an area we ought to give a real lift. They need it.

What is your thought?

Dr. Kreshover. I agree, sir.

FLUORIDATION

Mr. Fogarty. What about the problem of fluoridation? You mentioned nothing about that in your summary.

Was it in the prepared statement?

Dr. Kreshover. I went into it, sir.

I should like to say, Mr. Chairman, that very notable progress is being made in the area of fluoridation as a very important and proven method for caries control; that despite the unfavorable evidences of some recent referenda to the tune of defeats of fluoridation, anywhere from a 3-to-2 ratio, that we today have over 2,000 communities which are receiving the benefits of fluorides artificially added to their communal water supplies. This represents approximately 42 million people receiving these benefits today.

In addition to this we have approximately 7 million people receiving the benefits of fluoridation in naturally fluoridated communities; that is, communities where fluoride appears naturally in the water supply.

The fluoridation problem, however, is one which still has to be squarely faced in terms of a greater degree of receptiveness by our population. It has been estimated, as you perhaps know from the recent survey of dentistry, that were fluoride benefits available to all the population to which they could be applied there would be a saving each year of close to a half billion dollars which is otherwise spent by the average citizen, by our average citizen, for the repair of teeth which become carious. And so, I believe, we need a stepped-up program in terms of education of our people; second, I believe we have to have some behavioral science studies carried on in communities to attempt to determine more adequately why people do not accept health benefits which are available to them.

Mr. Fogarty. Some of this also is a matter of education.

Dr. Kreshover. It certainly is.

Mr. Fogarty. Many of the local dental societies can do more in this area than they are presently doing.

ANTIFLUORIDATION CLAIMS

Do you know of any medical or scientific evidence at all which has shown harm coming to anyone because of the use of fluorides in water supplies?

Dr. Kreshover. None whatsoever.

Mr. Fogarty. Why do these people make all these claims that it is harmful and poisonous; and some even say it is Communist inspired.

Dr. Kreshover. You can take an animal, give him a slug of a vitamin, let us say, or anything which would, under normal conditions, relate to the maintenance of good health, and by overdosage of almost anything conceivable you can cause harmful effects.

The arguments of the antifluoridationists are akin to this: You take a few carloads of sodium fluoride, dump it into a small amount of water, and obviously you will get untoward effects.

Mr. Fogarty. There are many places in the country whose drinking water has four or five times the amount of fluoride you use.

Dr. Kreshover. There is an excellent study to point this out in Texas, in Bartlett and Cameron. Bartlett has an extremely high content of fluoride in its drinking water, something in the neighborhood of eight parts per million.

On the other hand Cameron had practically an infinitestimal amount of fluoride.

We have done extensive studies in both of these communities and have demonstrated no untoward effects whatsover, both from the standpoint of the disease or from the standpoint of mortality. There is no relationship whatsoever between high fluoride levels in drinking water of communities and any disease process.

The only evidence of anything abnormal has to do with the mottled enamel through high concentration.

Mr. Fogarty. What were the arguments some years ago when chlorine was added?

Dr. Kreshover. The same for chlorine, polio vaccine, for anything that spells progress there will be some self-assured individuals who profess to know all of the answers and are ignorant of them. They are the ones who object. It takes an educational process to ultimately quiet them down.

FLUORIDATION OF DISTRICT OF COLUMBIA WATER

Mr. Fogarty. Have we had any problem in the District of Columbia?

Dr. Kreshover. Not to my knowledge, sir.

Mr. Fogarty. There were some people in Congress who were going to make quite a fight about it at the time, but nothing ever developed. Since it has been added to the water supply system here I have heard of no real problems.

Dr. Kreshover. I have not, either, sir.

Mr. Fogarty. That is a good sign, is it not?

Dr. Kreshover. It certainly is.

SURVEY OF DENTISTRY

Mr. Fogarty. This survey of dentistry I thought was one of the best surveys concerning this health problem I have ever read. Do you agree it was a good job?

Dr. Kreshover. I certainly do.

Mr. Fogarty. It pointed up many shortcomings. I was hoping you would be able to convince the Public Health Service and the Secretary that you should follow this survey and really do a good job. I thought you might convince them you ought to go forward but here you are with no increase in fellowships or training, and inadequate funds for research.

I wonder if anybody in the Bureau of the Budget took time to read that report? You would not know, of course.

INITIAL BUDGET REQUESTS

Will you supply for the record what you asked of the Department?

Dr. Kreshover. Yes, sir.

Mr. Fogarty. And what you asked of the Bureau of the Budget?

Dr. Kreshover. Yes, sir.

Mr. Fogarty. What you were given and what you were cut by both, and how these cuts will affect your program?

Dr. Kreshover. Yes, sir.

(The information requested follows:)

Impact of DHEW and Bureau of Budget decreases on program

[In thousands]

Obligations by activity	Preliminary estimate to Department of Health, Education, and Welfare	Change	Department of Health, Education, and Welfare to Bureau of the Budget	Change	1963 President's budget
Grants and related contracts:					
Research	$9,796	−$176	$9,620	−$497	$9,123
Fellowships	1,230	0	1,230	−348	882
Training	5,200	0	5,200	−1,459	3,741
Total grants and related contracts	16,226	−176	16,050	−2,304	13,746
Direct operations:					
Research	3,217	−243	2,974	−116	2,858
Review and approval of grants	358	+123	481	−57	424
Administration	216	−21	195	−24	171
Total direct obligations	3,791	−141	3,650	−197	3,453
Total obligations	20,017	−317	19,700	−2,501	17,199

GRANTS AND RELATED CONTRACTS

Research—decrease of $673,000 from final submission to DHEW

This decrease prevents the additional support of research projects in three fields. (New grants and supplemental requests).

1. Growth and development and congential anomalies research	$293,000
2. Periodontal disease research	280,000
3. Behavioral science research	100,000

Fellowships—decrease of $348,000 from final submission to DHEW

This decrease would prevent support of 39 additional fellows in the predoctoral, postdoctoral and special programs.

Training—decrease of $1,459,000 from final submission to DHEW

This decrease has the effect of holding the training grants program at the 1962 level. It would prevent the following:

(1) A $500,000 increase in the important dental student training program in the use of chairside assistants. The requests for program increases exceed the resources available in the President's budget.

(2) The raising of the level of support in the regular training grant program by $40,000 in each of 15 dental schools.

(3) The initiation of new programs in eight nondental school institutions at an approximate level of $45,000 for each.

DIRECT OPERATIONS

Research—decrease of $359,000 from final submission to DHEW

(1) Epidemiology and biometry program—decrease of $20,000. This would have been used to meet increasing statistical processing needs connected with the expanding biological research activities in genetics and other areas.

(2) Clinical investigations program—decrease of $82,000. This would have been used for the support of five positions and related other objects costs in connection with the oral pharyngeal and genetics research programs.

(3) Experimental pathology program—decrease of $65,000. This would have been used to support five additional positions and related other objects costs in experimental pathology.

(4) Payment to NIH management fund—decrease of $192,000.

Review and approval of grants—decrease of $57,000 from DHEW submission to Bureau of the Budget

This decrease would prevent the support of three grants review positions and related travel and other objects costs. These positions would be necessary to support expanded grants programs.

Administration—decrease of $45,000 from final submission to DHEW

This decrease would prevent immediate recruitment of two program analyst positions requested in the President's budget. Funds in that budget would not permit recruitment before one-half of the fiscal year had elapsed. An additional position would have been supported in the submission to the Department.

Mr. FOGARTY. Mr. Marshall?

CURRENT PERSONNEL

Mr. MARSHALL. On page 214 of the justifications I note that you had 181 permanent positions last year and the estimate shows 247 permanent positions for 1962. How many of those 247 positions are now filled?

Dr. KRESHOVER. 214.

10-YEAR GROWTH OF APPROPRIATION

Mr. MARSHALL. I notice on page 217 of the justification that in 1953 you had an appropriation of $1,650,000.

Dr. KRESHOVER. That is right.

Mr. MARSHALL. In 10 years' time that appropriation has risen to the point where the estimate this year is for $17,199,000, is that correct?

Dr. KRESHOVER. Yes, sir.

Mr. MARSHALL. That is all, Mr. Chairman.

Mr. FOGARTY. Is there anything else you wish to say, Doctor?

Dr. KRESHOVER. No, sir; except to thank you very much for treating me so kindly. As a newcomer I appreciate it very much.

Mr. FOGARTY. You have done a fine job.

(The following was submitted for the record at the request of the committee:)

DISABILITY AND COST OF DENTAL DISEASES

Statistics of the annual number of deaths and total current number of disabilities caused by each of the major diseases dealth with in the Dental Institute, and the estimated annual cost to the Nation.

1. Deaths related to dental disease

No information available.

2. Disabilities caused by dental diseases

Dental caries is the most prevalent of all diseases, affecting more than 9 persons in 10, and over 90 percent of school age children. Diseases of the supporting bone and gingival tissue affect at least half of the population by age 50 and almost all by age 65. One child in 10 has some form of malocclusion, and those born with cleft lips and palates are accumulating at a rate of approximately 8,000 per year.

3. Estimated annual cost to the Nation

It is estimated that the 180 million people in the United States in 1960 had accumulated at least 700 million unfilled cavities. This enormous accumulation of untreated teeth far exceeds the capacity for treatment. Family expenditures for treatment services total $2 billion annually, or 15 cents out of every dollar spent for personal health services.

Dental disorders are progressive, cumulative, and require more treatment time than is available in an already scarce profession. The shortage of dentists, coupled with higher treatment costs, an expanding population, a high prevalence of oral diseases, and a lack of public understanding of oral health problems combine to pose a major public health problem. Although a concerted effort is underway to augment the number of dental practitioners available in order to reduce the disparity between needs and corrective capacity, present evidence seems to indicate that the situation will become more acute in the foreseeable future.

HIGHLIGHTS OF RESEARCH CONDUCTED BY THE NATIONAL INSTITUTE OF DENTAL RESEARCH, 1961

INTRODUCTION

The increased scope and depth of dental research during this past 10 years has provided a better understanding of the complex forces that cause or otherwise influence oral diseases. For example, in studies of tooth decay during this period seemingly unrelated investigations in bacteriology, biochemistry, and genetics have been joined by inquiring minds to form the present picture of dental caries as an infectious, transmissible disease. New and better laboratory facilities, occupied in May 1961 by the Dental Institute, now provide an even better opportunity to bring together scientists from different disciplines to accelerate the progress of dental research. Planned expansion has proceeded rapidly in many sectors of the Institute's intramural program, including new research units for the study of enzyme and protein chemistry and the establishment of a section to study development and function of the regions of the mouth, pharynx, and larynx.

The following report will discuss some of the current highlights of research progress from the Bethesda Laboratories of the National Institute of Dental Research.

DENTAL CARIES

As long as dental decay has existed—and it dates back at least to the glacial age—theories have been advanced to explain its etiology and pathogenesis. Today, as never before, these theories are being substantiated or challenged by important knowledge of structural characteristics and biochemical and other properties of teeth. However, the accumulation of scientific knowledge now available indicates that, for dental decay to occur, a tooth must first be predisposed or susceptible to attack; second, there must be present a type of oral bacteria—not clearly defined, but nevertheless necessary; and third, there must be certain nutritional requirements for the bacteria, generally thought to be high in carbohydrate.

Experimentally induced lesions

Several years ago scientists at NIDR discovered that certain strains of hamsters, thought to be naturally resistant to caries, developed decayed teeth when housed in the same cage with caries-susceptible hamsters. This indicated that caries was transmissible from animal to animal and that the so-called resistant hamsters owed their lack of decay to the absence of some agent that would cause caries. Further work showed that dental caries could be prevented in future generations by adding penicillin to the diet of breeding females. This suggested that the responsible causative agent, or agents, might be bacteria killed by the antibiotic.

In subsequent studies with conventional animals a specific strain of streptococci proved able to induce caries when introduced in pure culture into the mouths of noninfected hamsters, animals so-called because they were known not to harbor a caries-producing flora. Lactobacilli, diphtheroids, yeast, fusiforms, and other types of streptococci produced no dental decay when introduced alone or in combination. Since several of these noncariogenic micro-organisms produced acid in the oral cavity, decay-producing bacteria could not be distinguished solely on the basis of their ability to produce acid.

In all of these experiments the animals received a diet rich in carbohydrates—conducive to caries—so that the presence or absence of the cariogenic streptococcus became the sole determinant of whether or not the animals developed dental caries.

Similar findings also were made in the case of germfree rats, where a single strain of streptococci was also found to be specific for the production of caries. However, this particular streptococci was not pathogenic in the hamster. Thus, it now appears that various animals may have their own specific pathogen for dental caries. These experimental findings also reaffirm previous laboratory evidence that, as an infectious and transmissible disease, dental caries is far more specific than scientists realized and is highly dependent on the critical interaction between host, diet, and microflora.

Influence of protein on dental decay

A number of laboratory studies on dental decay have sought to determine the influence of protein on the caries process. For example, after earlier findings that dental decay could be produced in white rats by diets containing heat-processed cereals and heat-produced skim milk powders, it was shown that the addition of the essential amino acid lysine effectively inhibited the development of decay lesions. In similar fashion, high caries levels were produced with a diet containing whole millet flour in the complete absence of sugar. These findings have further emphasized the influence of dietary factors beyond the carbohydrates into areas of protein and essential amino acids.

Influence of mineral phosphates on dental decay

In related studies of chemical inhibiting agents, NIDR scientists have shown that dental decay in animals can be effectively reduced by adding certain mineral phosphates to the diet. These observations provided the basis for an extensive clinical study now underway in this country to assess the effects of dicalcium phosphates on human caries. If this compound, which appears to act locally on exposed surfaces of the teeth, should prove successful in reducing human caries, it would offer a dietary means of controlling dental decay where water fluoridation is not feasible.

FLUORIDE STUDIES

Tablet form of administration

NIDR scientists recently reported findings in a 12-year study of the efficacy of fluoride administered in tablet form. In this study, the dental caries experiences of over 100 children who ingested 1 milligram of sodium fluoride, in tablet form, every day for an average two-thirds of their lives, were found to be comparable to the amount of decay previously reported for children of similar ages who drank fluoridated water. Although water fluoridation remains a more practical and dependable procedure for caries control, these findings suggest a solution to those situations where, because of geographic remoteness and the like, conventional fluoridation is not practical.

Topical fluoride treatment

The exact manner by which locally applied fluoride compounds confer protection to teeth is not completely understood. However, NIDR scientists, using electron and X-ray diffraction techniques, have recently reported the isolation and identification of a substance that forms on the surface of teeth following exposure to stannous fluoride solutions. The increased acid resistance is due in large part to the deposition of a protective surface over the enamel. Samples of the deposit have been isolated and identified as hydrous hydrated stannous oxide, which are very resistant to washing with water, etching, and brushing with water alone but quite readily damaged by brushing with an abrasive.

Fluoride-citrate studies

In still another area of fluoride research, clinical studies at NIDR have shown that an inverse relation exists between the fluoride and citrate content of bone in individuals consuming varying amounts of naturally occurring waterborne fluorides over an extended period of years. These findings have reecntly been substantiated by laboratory studies in which the concentration of bone citrate in experimental animals decreased as the fluoride content of drinking water was increased.

It now appears possible that this fluoride-citrate relation in the developing tooth may also play an important role in the carious process.

GROWTH AND DEVELOPMENT

Influence of prenatal factors on dental decay

In still another approach to a better undertsanding of dental decay, a new program was recently undertaken at NIDR to determine the effects of various prenatal factors on the caries experience of offspring in animals. It has been found, for example, that rats rendered acidotic during different stages of pregnancy deliver litters with a markedly increased susceptibility to dental decay. In one experiment the offspring of animals subjected to a 30-percent carbon dioxide/70-percent oxygen atmosphere early in pregnancy developed a severity of caries that was twice that observed in the offspring of untreated control animals. On the other hand, exposure during the latter period of pregnancy had no apparent effects on the caries rate of the young. Additional biochemical and morphological studies may provide a clearer understanding of this congenitally acquired susceptibility of dental tissues to attack.

Experimentally induced congenital anomalies

It is only within recent years that any appreciable attention has been directed to prenatal influences on mouth and tooth development. Certainly, the rather common deformities of harelip and cleft palate have presented an incomplete picture with respect to their etiology. In some instances they are unmistakably related to defective genetic composition, whereas in others, a clearly defined environmental factor exists. Although clinical studies are most essential to elucidate the causes of harelip, cleft palate, and other defects of oral development, significant advances in knowledge have been gained through studies with laboratory animals. For example, in one NIDR study the effects of oxygen deprivation on the production of congenital deformities were studied by inducing anoxia directly in the fetuses of rats. Another experiment dealt with the effects of increased amniotic pressure on fetal development. In both of these continuing studies, a high incidence of palatal clefts, limb deformities, and fetal resorptions were observed.

Calcification

The process of mineralization within the body is of particular interest to dental and medical scientists; however, the underlying factors that regulate normal and pathological calcification in certain tissues are still not clearly understood.

In a series of studies specimens of normally noncalcifying tissues (rat tail, skin, etc.) were implanted into the peritoneal cavity of young rats. Investigators found that these tissues, removed atfer several months, had undergone mineralization. This was confirmed by X-ray diffraction analysis.

These findings served as a basis for further in vivo studies of mineralization using tissue preparations implanted in dialysis bags and in combination with certain agents thought to influence calcification. When various collagenous tissues were implanted in rats in sealed dialysis bags, it was found that some specimens became calcified, while other samples did not. Those implants which mineralized had been contaminated with bacteria during preparation, and those that failed to mineralize had remained sterile. As a result, the investigators turned their attention to studies of individual species of micro-organisms, to determine whether such bacteria would calcify when implanted alone.

Results from these experiments showed that dead organisms calcified in a shorter time than did living organisms, but in both instances the ultimate presence of hydroxyapatite was confirmed by X-ray diffraction. Electron microscopy revealed striking similarities between the mineral deposits recovered from intraperitoneal transplants of tissues and bacteria and those obtained from developing human oral calculus.

Although these findings did not implicate any specific micro-organisms, they do support the contention that bacteria play an important role in the mineralization of dental deposits. Continuing studies at NIDR will utilize similar technics to assess the calcifying potential of saliva.

PERIODONTAL DISEASE

Experimental infection with oral bacteria

Studies of experimental infections with oral micro-organisms related to periodontal disease have been reported recently by NIDR scientists. In this series of investigations attention was focused on the isolation, purification, chemical analysis, immunological reactivity and physiological effects of bacterial endotoxins, and conditions in physiological processes that might contribute to the progress of periodontal disease. For example, endotoxins have been isolated for the first time in pure state from all of the major micro-organisms implicated in periodontal disease and specific histotoxic effects have been demonstrated in rabbits. Our scientists thus believe that in view of the present kynowledge of subtle, long-term systemic effects of bacterial endotoxins, the considerable amounts estimated to be present in the oral cavity might well have a broader significance for general health than their contribution to the inflammatory process and soft tissue lesions seen in periodontal disease.

Alveolar bone loss in animals

In studies to evaluate certain clinical impressions of periodontal disease, NIDR investigators have recently reported significant information on the nature of the disease, as well as the causative roles of nutrition and heredity. For example, a study of periodontitis in mice revealed a significant reduction in alveolar bone loss in an experimental group maintained on a high-protein diet, whereas a control group not on a supplemented diet showed no such protective effect. Of the two strains of mice observed, one was highly susceptible to the disease and the other relatively resistant, thereby indicating a genetic influence on susceptibility.

GENETIC STUDIES

Clinical research at NIDR is chiefly concerned with determining the underlying biological processes of oral diseases, with finding more successful methods for the prevention and treatment of these diseases, and with gaining a better understanding of disease processes in general. Since many of the oral diseases have a hereditary component, considerable attention has been given to the area of human genetics.

Japanese study

During the past 2 years, the NIDR actively participated in a child health survey in Hiroshima and Nagasaki under the sponsorship of the U.S. Atomic Energy Commission, the Rockefeller Foundation, and the Association for Aid to Crippled Children. The primary purpose of the survey was to study the effects of inbreeding in a large population where complete and detailed records of parents and offspring existed. The Japanese groups met these particular criteria, and their selection was coincidental and unrelated to any radiation effects associated with the atomic explosions during World War II.

Using facilities of the AEC and with the cooperation of the Japanese National Institute of Health, a team of examiners comprised of geneticists, pediatricians, dentists, and anthropologists examined a large number of children from first cousin marriages. Included in this group of some 5,000 children were records of many who were deceased. While all data have not yet been evaluated, there appears to be a significant death rate of almost twice that seen in a Japanese control group. Preliminary findings from dental examinations also indicated a higher frequency of supernumerary teeth than is reported for Caucasians and an accelerated eruption of permanent teeth.

U.S. population studies

In other genetic studies of a triracial isolate group in southern Maryland, NIDR scientists have continued to gather data on the prevalence, mode of inheritance, clinical manifestations, and other factors peculiar to the hereditary illnesses found in that population. Examples of recent findings include a frequency of dentinogenesis imperfecta (missing and malformed teeth) and albinism that is the highest reported for any population, a frequency of sickle cell trait that is the highest reported outside of Africa, evidence that certain speech defects are genetically determined, evidence of a hereditary factor that contributes to the prevalence of goiter, and detection of an abnormal protein in the matrix of teeth with opalescent dentin.

In the study of another selected inbred population group in North Carolina an estimate of fertility was reported as being the highest for any known racial or ethnic group in the United States; the ratio of children under 5 years of age per 1,000 women is 825 as compared with U.S. averages of 417. Also, from this population has come the first description of a hereditary disorder involving the faulty development of the epidermis of oral mucosa. Termed as hereditary intraepithelial dyskeratosis, the disease is characterized by lesions on the buccal mucosa, floor of the mouth, side of the tongue, as well as the bulbar conjunctive. Examination failed to reveal any evidence that it was due to a local environmental factor such as an allergen or occupational hazard. Other findings also tended to eliminate viruses, vitamin deficiences, and microbial infections as the responsible factors.

MONDAY, FEBRUARY 19, 1962.

ARTHRITIS AND METABOLIC DISEASE ACTIVITIES

WITNESSES

DR. FLOYD S. DAFT, DIRECTOR, NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES

RICHARD L. SEGGEL, EXECUTIVE OFFICER, NATIONAL INSTITUTES OF HEALTH

Object classification

[In thousands of dollars]

	1961 actual	1962 estimate	1963 estimate
11 Personnel compensation:			
Permanent positions	$3,712	$4,075	$4,267
Positions other than permanent	67	128	128
Other personnel compensation	45	46	46
Total personnel compensation	3,824	4,249	4,441
12 Personnel benefits	405	454	472
21 Travel and transportation of persons	216	340	344
22 Transportation of things	57	67	67
23 Rent, communications, and utilities	77	91	92
24 Printing and reproduction	14	19	19
25 Other services	900	657	621
Payment to "National Institutes of Health management fund"	3,620	4,492	4,860
26 Supplies and materials	638	740	775
31 Equipment	378	630	791
41 Grants, subsidies, and contributions	48,254	64,995	79,456
Subtotal	58,381	76,734	91,938
Deduct quarters and subsistence charges	16	17	17
Total obligations	58,365	76,717	91,921

Personnel summary

	1961 actual	1962 estimate	1963 estimate
Total number of permanent positions	549	598	622
Full-time equivalent of other positions	9	14	14
Average number of all employees	504	531	543
Number of employees at end of year	510	590	610
Average GS grade	8.2	8.3	8.3
Average GS salary	$6,980	$7,265	$7,265

Program and financing

[In thousands of dollars]

	1961 actual	1962 estimate	1963 estimate
Program by activities:			
1. Grants and related contracts:			
(*a*) Research	$39, 386	$54, 293	$68, 754
(*b*) Fellowships	570	1, 177	1, 177
(*c*) Training	8, 298	9, 525	9, 525
Total, grants and related contracts	48, 254	64, 995	79, 456
2. Direct operations:			
(*a*) Research	8, 383	9, 585	10, 173
(*b*) Collaborative studies	373	650	650
(*c*) Review and approval of grants	858	1, 145	1, 337
(*d*) Administration	218	265	305
Total, direct operations	9, 832	11, 645	12, 465
Total program costs [1]	58, 086	76, 640	91, 921
Change in selected resources [2]	279	77	
Total obligations	58, 365	76, 717	91, 921
Financing:			
Comparative transfers to other accounts	243		
Unobligated balance lapsing	2, 592	5, 085	
New obligational authority	61. 200	81, 802	91, 921
New obligational authority:			
Appropriation	61, 200	81, 831	91, 921
Transferred to "Operating expenses, Public Buildings Service," General Services Administration (75 Stat. 353)		−29	
Appropriation (adjusted)	61, 200	81, 802	91, 921

[1] Includes capital outlay as follows: 1961, $378,000; 1962, $630,000; 1963, $791,000.

[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders, 1960, $247,000 (1961 adjustments −$4,000); 1961, $522,000; 1962, $599,000; 1963, $599,000.

Mr. FOGARTY. Dr. Daft, do you have a statement for the committee on arthritis and metabolic diseases?

Dr. DAFT. Yes, Mr. Fogarty.

Mr. FOGARTY. Go right ahead, Doctor.

GENERAL STATEMENT

Dr. DAFT. I believe, Mr. Fogarty and members of the committee that an opening statement has been submitted for the record.

(The statement referred to follows:)

STATEMENT BY DIRECTOR, NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, PUBLIC HEALTH SERVICE, ON "ARTHRITIS AND METABOLIC DISEASE ACTIVITIES"

Mr. Chairman and members of the committee, the current fiscal year marks another milestone in the progress of this Institute toward realization of our ultimate aim, the attainment of optimum health for the largest possible proportion of our people. In this year's statement I want to relate to you our most recent attainments and program developments. The past year has been a particularly productive and rewarding one; the studies of our scientists and grantees have continued to progress along lines of study established during previous years, while research excursions have been successfully pushed into new territories which have previously resisted investigative efforts.

We shall review with pride our research accomplishments for the past year. The significance of the more applied results of our work will be evident. Fully as significant are the attainments of the more fundamental aspects of our program upon which will rest tomorrow's clinical advances. I am particularly pleased to state that the National Institute of Arthritis and Metabolic Diseases has made a special, and I believe productive, effort toward solution of the problems in which the committee has shown particular interest as a result of our testimony last year. The advances to be described in greater detail later have resulted from research pursued in our own laboratories in Bethesda in the many nongovernmental institutions throughout the country which receive support from this Institute in the form of specific research project grants.

In rheumatoid arthritis additional knowledge has accumulated in the all-important sphere of the immunologic aspects of this disease. Increasing evidence is accumulating that an immune mechanism may be the basic cause of this disorder, and that a large number of diseases previously not necessarily suspected of being related to rheumatoid arthritis are likewise clinical manifestations of an aberration of man's immune mechanisms. Our understanding of possible hereditary and environmental factors involved in the disease picture has also grown in the last year. During this last year it has been possible to establish the precise cause of the acute disabling attacks of gout and further to perfect its successful treatment and prevention. This year we can report an important step forward in the control of diabetes by the use of combinations of oral drugs; new developments in this area, in which our scientists and grantees have been so active, have extended the benefits of effective therapy to thousands of diabetes patients who heretofore did not respond to the conventional method of treatment with single antidiabetic oral drugs, and who had to rely on daily insulin injections for proper control of their disease. Also in the field of diabetes, additional knowledge has been obtained on the method of action of these oral drugs, and new insight has been gained into some of the most fundamental aspects of this disorder, especially its all-important connection with diabetic kidney disease. Very satisfactory and practical strides have been made in the field of gastroenterology; here a new type of treatment was found to relieve patients with biliary cirrhosis, a new method was developed to foretell the possibility of postoperative "dumping syndrome" in patients suffering from peptic ulcers and here, too, important refinements have been developed in the detection of strangulated intestinal obstruction and in its successful nonsurgical manipulation. Steady progress has been made in the area of cystic fibrosis, both in our understanding of the fundamental processes involved in this disorder as well as in the practical relief which can be extended to the youthful victims of this dread disease.

Very exciting findings in the field of fundamental research were obtained in our laboratories in Bethesda where our scientists succeeded in partially "cracking the genetic code"—in unmasking and characterizing one of the most important specific mechanisms through which the two hereditary cell materials DNA and RNA act to code information and carry it from cell-generation to generation and direct the building of specific protein molecules in living matter.

Also this year, special efforts have been made to insure that the research findings of our scientists and grantees are communicated to the practicing physician at the earliest possible moment so as to obtain early dividends in improved medical care. At this point I would like to describe in greater detail the advances which have resulted from work done during the past year.

ARTHRITIS AND RHEUMATIC DISEASES

Through the testimony of previous years and through special reports submitted, the committee has become aware of the increasing importance attached by knowledgeable researchers in the field to the immunologic aspects of rheumatoid arthritis.

I will try to summarize in a few sentences the present state of our knowledge concerning this possible causative aspect of rheumatoid arthritis without recapitulating the very voluminous data on the subject, some of which has already been presented on previous occasions.

In recent years it has become an increasingly plausible hypothesis that rheumatoid arthritis results from a state of hypersensitivity or, if you please, is due to aberrant immune reaction taking place in certain tissues of the body, notably the joints. According to this concept it is possible for an individual to elaborate antibodies (protein substances which normally provide protective immunity against specific noxious agents) against sensitizing substances (antigens). These may be of exogenous origin or may even be of normal endogenous origin but have been altered in some way so that they have acquired the ability to act antigenically. The resultant antigen-antibody reactions in various tissues of the body then give rise to the pathological changes characteristic of the disease.

A unique substance, the "rheumatoid factor," found in the serum of patients suffering from rheumatoid arthritis, has been described previously. It has been used as a tool in a number of diagnostic tests devised for rheumatoid arthritis in our own laboratories or by grantee scientists. In recent work it has been found that the rheumatoid factor has the characteristics of true antibodies, and it has become increasingly certain that it results from a hypersensitivity phenomenon. The question at the present time is "what is the nature of the postulated antigen, the deleterious substance which stimulates the synthesis of the rheumatoid factor in certain tissues of the body, and which initiates the chain of abnormal immune reactions which culminates in the crippling joint damage characteristic of rheumatoid arthritis?"

At the present time extensive research efforts are being made on the immunologic aspects of rheumatoid arthritis and its related rheumatic and connective tissue diseases. About one-third of all research in arthritis is devoted to this approach, and indeed considerable progress has been made even during the brief period since last year's testimony. Details and a comprehensive presentation of significant studies and their results are given in a special report on the subject of arthritis and hypersensitivity prepared by this Institute for information of the Congress. A few other studies are briefly mentioned here.

In a highly significant cooperative study conducted in our laboratories in Bethesda and at the Rheumatism Research Center of the Manchester Royal Infirmary in England, it was established that serologic tests for the rheumatoid factor in arthritis patients can give physicians prognostic as well as diagnostic information. This study, which involved a large series of patients and spanned 10 years, demonstrated conclusively that patients who have a positive serologic sheep cell agglutination test (SCAT)—for the presence of rheumatoid factor—also display an increased long-term mortality, increased internal organ and tissue destruction, and severe crippling. On the other hand, patients with SCAT-negative rheumatoid arthritis have a normal mortality rate, a high incidence of remission of the disease, few internal lesions, and little bone damage. In general, SCAT-negative patients were found to respond well to the more conservative methods of therapy—bed rest, physiotherapy, and salicylates, while the positive group often failed to respond to any measure other than corticosteroids.

That genetic factors may also be involved in the basic causes of rheumatoid arthritis was indicated by a study by scientists of this Institute involving relatives of patients with Sjogren's syndrome, a disorder related to rheumatoid arthritis. This investigation revealed that a significant, high percentage of close blood relatives of patients with this disease have manifestations of rheumatoid arthritis.

In a study with important clinical significance for the long-term treatment of patients with rheumatoid arthritis who are receiving corticosteroid therapy, Institute scientists developed a prophylactic diet which protects the skeletons of these patients from damaging demineralization. Experience with corticosteroid therapy has shown that long-term use of these compounds in many cases leads to a loss of calcium from the bones followed by an overall decrease in the calcium content of the body through urinary excretion of this calcium. Continued demineralization of the skeleton during prolonged steroid treatment may pose a considerable problem to patients through weakening of individual bones and eventual fractures or deformity of the spine. Work at the Clinical Center in Bethesda has now shown that this drug-induced excessive calcium loss from the body may be prevented, and indeed in some cases significant skeletal calcium storage may be produced, by increasing the dietary calcium intake to relatively high levels.

GOUT

We can point to particular progress in the area of gout where significant contributions were made during the past year. As the committee has heard in previous testimony, the basic defect in gout which underlies its clinical symptomatology is an abnormal accumulation of uric acid in blood and tissues, either due to a pathologically enhanced uric acid production or as the result of an impairment in its excretion by the kidney. Recently, scientists in Bethesda were able to elucidate the mechanism responsible for the acute disabling attacks of gouty arthritis by demonstrating that the injection of microscopic, needle-shaped sodium urate crystals into the joints of volunteers will produce typical gouty attacks characterized by an acute inflammatory reaction with pain, redness, tenderness, fluid accumulation, and a leukocyte response in the affected joints. These findings are in sharp contrast to the accepted belief that urate salts (which tend to deposit in tissues in gouty patients) are inert and have little to do with the acute painful attacks of this ancient debilitating disease.

In the area of diagnosis of gout, Institute scientists discovered that through their tendency to block the elimination of uric acid by the kidney, salicylates (such as aspirin) may cause abnormally high blood uric acid levels. Since elevated blood uric acid levels are an important diagnostic indicator in gout, this may lead to mistaken diagnoses of gout in individuals with acute joint pain who have taken salicylates for alleviation of their pain before presenting themselves to a physician. The possibility of such a diagnostic "red herring" was worked out when the National Institute of Arthritis and Metabolic Diseases investigators were able to establish that several patients, presented to them as allegedly suffering from gout, were really victims of rheumatoid arthritis.

In another series of experiments, Institute scientists demonstrated the effectiveness of sulfinpyrazone, a compound related to an earlier antirheumatic drug, phenylbutazone, as an agent which promotes the rapid excretion of uric acid from the body. The uricosuric action of the new drug was shown to be more potent than that of probenecid which had been in use heretofore; moreover, the new drug has been proven effective in cases where patients did not respond to probenecid.

Also during the past year, Institute grantees at Mount Sinai Hospital in New York have summarized the results of their investigation of the efficacy of colchicine in preventing recurrent gouty arthritis over a period of from 2 to 10 years in 208 patients selected because of a prior history of frequent and disabling attacks of acute gouty arthritis. In the hands of these investigators, using specific dosage schedules, the prophylactic use of colchicine proved not only extremely effective (responses were: 74 percent excellent, 20 percent satisfactory, 6 percent unsatisfactory), but generally safe and devoid of untoward side effects.

We may indeed look upon gout as one form of arthritis which has progressively yielded ground to a relentless research attack, and which has now become a reasonably manageable disorder.

DIABETES

Here again a two-pronged attack continues against this best known and most important of the metabolic diseases. On one hand, efforts continue to improve the care of the diabetic patient by evaluating the long-term effects of different currently available treatments, and by the introduction of important new improvements into oral antidiabetic therapy. On the other hand, fundamental aspects of diabetes are being investigated, notably its basic biochemical derangement of body metabolism; the specific actions of insulin and its counterhormone, glucagon; the relationship of the liver to these two substances; the fundamental pathologic changes in the diabetic kidney; and the specific method of action of the oral hypoglycemic drugs. The value of this research, although intended to solve the problems of clinical diabetes, reaches far beyond this goal, since insulin is only one of the many endocrine secretions of the body, all of which are potent chemical mediators. Since these hormonal secretions are interdependent and their activities interdigitate, it is probable that a study of the basic facts of insulin action will lead to other fundamental knowledge applicable to important problems in the general field of internal diseases.

In the clinical area, I am particularly happy to describe what we consider a significant step forward in the treatment of ketoacidosis-resistant patients, those patients who generally have acquired the disease in adult life and in whom disorder is found in a stable form (in contrast to juvenile diabetes which is considered the most unstable and ketoacidosis-prone manifestation of the disease). From previous testimony the committee is well aware that within the past several years the oral antidiabetic drugs have had a tremendous impact upon the treatment of diabetes. Available in easily administered tablet form, these drugs have replaced onerous daily insulin injections in more than a third of the Nation's 1½ million diabetics who are under active treatment. However these drugs are not the complete answer to the problem of diabetes therapy since they are mostly effective in mild, stable, and recently acquired cases of diabetes.

The three oral drugs now in use were developed by the pharmaceutical industry abroad and in the United States, and each shares insulin's ability to lower the abnormally high blood sugar levels characteristic of diabetes. The first two hypoglycemic drugs known, tolbutamide and chlorpropamide, belong to a class of compounds known as sulfonylureas (they are distantly related to the sulfa drugs, and it was in the testing of experimental sulfonamides that the blood sugar lowering action of the sulfonylureas was first discovered). Tolbutamide, when effective in maintaining normal blood sugar levels, may be the drug of choice in the adult, stable ketoacidosis-resistant form of diabetes. In a substantial proportion of cases, however, it fails either to achieve the desired low blood-glucose levels or to maintain this action after prolonged periods of therapy. Although chlorpropamide, the second sulfonyluria found, is more potent and longer acting than tolbutamide and has proven its effectiveness in some tolbutamide-resistant diabetics, its use entails a small but definite risk of toxic side effects and hypoglycemic reactions. The third and latest of the oral drugs is phenformin which differs from the sulfonylureas both in its chemical structure and its method of action in the body.

I am now in a position to report in detail on a development of considerable value which I mentioned only briefly last year. In the hope of increasing the usefulness of the oral hypoglycemic drugs, Institute grantees at Boston University, and the Veterans' Administration hospital, Dallas, and Southwestern Medical School, have been testing various combinations of these agents in oral drug-resistant diabetic patients. They have now found that by combining the latest drug, phenformin, with one of the older sulfonylureas, they can adequately control many diabetics who previously did not respond to either of the drugs alone. The combination of a sulfonylurea drug with phenformin—in smaller doses than those required to obtain an antidiabetic effect when each drug is used alone—was found to avoid the therapeutic failures of single-drug therapy while enjoying a wider margin of safety with considerably reduced side effects.

Apparently the combination of the two classes of drugs is additive with respect to their desirable hypoglycemic action, but not with respect to their untoward side effects. Many of the gratifying responses to combination therapy occurred in extremely difficult patients in whom prior therapy with tolbutamide, other oral hypoglycemic drugs, and even insulin had been unsatisfactory. Combination therapy appears to be the most potent of the oral antihyperglycemic regimens tested so far, and makes adequate control with oral drugs a possibility for most ketoacidosis-resistant diabetics in whom single oral agents have been unsuccessful.

These findings are particularly gratifying since extensive clinical evaluations carried out by grantee scientists, and reported to the committee last year, had turned up increasing evidence that individual patients may become resistant to he oral antidiabetic drugs and that the percentage of secondary failures (failure of hypoglycemic action after a particular drug originally proved efficacious in controlling the patient's diabetes) may increase with prolonged oral drug therapy. It appears now that combination therapy may provide an effective answer to such cases of secondary failure.

In fundamental studies, Institute grantees from the University of Chicago have thrown light on the site of synthesis of insulin's "counterhormone," glucagon, and have spotlighted its possible role in the causation of the abnormally elevated blood lipid levels which are part of the disease picture of diabetes. Other studies by Institute grantees at Western Reserve University have demonstrated that insulin undergoes a distinct modification, possibly in the liver, before it acts in facilitation of glucose uptake by tissue cells.

Significant studies by a grantee investigator at the Jewish hospital in St. Louis have directed our attention to a hitherto unsuspected mechanism which may underlie the vascular damage, particularly in the kidney, which often accompanies diabetes of long standing. A comprehensive, detailed presentation of these and other studies is found in a separate special report on diabetes, prepared by this Institute for information of the Congress.

Another facet of diabetes activities in which I think the committee will be interested is destined to aid greatly investigators of this disease everywhere. I refer to the establishment of a comprehensive diabetes abstract-microcard-translation-retrieval system which is being supported by this Institute and is being sponsored by the American Diabetes Association. I need not emphasize too much before this group the importance of effective communication in the field of biomedical research. It is hoped that this system which combines facilities for collecting and abstracting all scientific diabetes data published anywhere, their translation if necessary, and their coding and incorporation into a storage and retrieval system, will effectively support all current and future research efforts in the field of diabetes. At the present time, an abstract editor at the University of Rochester is studying the sources of all diabetes-related literature, and the documentation center at Western Reserve University is preparing a sample group of abstracts; detailed work is also in progress to develop the necessary codes which will be suitable for retrieving the stored diabetes related data and literature.

GASTROENTEROLOGY

The importance of gastrointestinal disorders in the overall picture of the Nation's health cannot be emphasized enough. Diseases of the gastrointestinal system rank second only to heart disease in the frequency of physician house and office visits required. In recent years there has been renewed and productive interest in research in the gastrointestinal field; a not insignificant proportion of this renaissance was stimulated by support from this Institute, and by the current major expansion in the variety of disciplines from which problems in gastroenterology can now be approached. At this point, I would like to mention a recent study by grantees at St. Luke's Hospital and Columbia University in New York, which illustrates not only practical, clinically applicable progress in the treatment of a specific disease in this general field, but again emphasizes the useful principle whereby findings in one area of biomedical research may become helpful adjuncts in solving problems in another unrelated field of study.

Intractable itching is usually a major complaint of patients with biliary cirrhosis, a disease resulting from interference with normal bile excretion. Until recently, management of this pruritus, presumed to be due to the deposition of dammed-up bile acids in the patient's skin, has been very unsatisfactory. The pruritus can be so severe and unremitting that the patient may become temporarily psychotic and even contemplate suicide. An effective drug for alleviation of this serious manifestation of the disease has now been found. In a clinical study of the possible application of an anion exchange resin (MK–135) manufactured by Merck & Co., Inc., our grantee scientists found that this material may act as a potent bile acid sequesterant with a marked proclivity for forming insoluble complexes with bile acids in the gastrointestinal tract. These complexes not only prevent the absorption of bile acids but tend to mobilize the abnormal accumulations of bile salts from the skin, thereby bringing about effective relief of the severe itching.

In connection with the study a direct relationship was observed between the amount of the resin ingested by the patients and their blood cholesterol level. It is unnecessary, I am sure, to elaborate on the suspected role of abnormally high beta-lipoprotein and blood cholesterol levels in the genesis of atherosclerosis and its major complications such as coronary heart disease. Suffice it to say here that in subsequent experiments this resin was successful in reducing serum cholesterol levels significantly not only in patients with abnormally elevated blood cholesterol values due to established coronary heart disease, diabetes, and familial hypercholesterolemia, but also in normal subjects whose control levels of serum cholesterol levels were already low by American standards. Since it is well known that bile acids are major end products of normal cholesterol metabolism, and since cholesterol is probably an important precursor of bile acids, the incidentally observed blood cholesterol-depressing effect of the resin was readily explainable. In addition to having provided a clinically efficacious remedy for the profound itching of patients with biliary cirrhosis, these studies have opened up a new avenue of approach to another important field of research in which related investigations are now continuing.

One of the most important subjects in the field of gastroenterology is that of peptic ulcer. Approximately 1 male out of 10 in the American population suffers from peptic ulcer symptomatology, either sporadically or chronically. In a large number of cases, peptic ulcer symptomatology eventually leads to surgery involving duodenal and gastric resection. Although this surgery may ultimately bring relief to the patient, a certain percentage of gastric resections are eventually followed by an undesirable complication commonly known as the dumping syndrome. Institute grantees at the College of Medical Evangelists have greatly advanced our understanding of the basic mechanism underlying this complication and have developed a preoperative test which makes it possible to predict whether or not a given patient is apt to have any serious problem after gastric surgery and what specific surgical procedure from among the various choices available may be best suited to a given patient.

Another productive study by Institute grantees at the Jefferson Medical College and Hospital in Philadelphia also concerns the possible postoperative complications of peptic ulcer surgery. Impaired absorption of fat with steatorrhea (fatty stools) has been noted in about 50 percent of patients subjected to a Billroth II type of subtotal gastric resection for benign peptic ulcer. The steatorrhea is occasionally of a severe degree and is among the common causes of malnutrition so frequently encountered in post-gastrectomy patients. A variety of hypotheses has been advanced by investigators concerning the cause of this faulty fat absorption.

In a series of experiments involving the simultaneous study of intestinal fat absorption and intestinal bacteriological examinations in normal and post-gastrectomy patients, the NIAMD grantees succeeded in establishing a close correlation between extremely high bacterial loads in intestinal segments bypassed by the operation and the impaired ability of patients to absorb fat. The study strongly indicates that excessive bacterial growth in surgically created, stagnant intestinal "backwater" segments interferes with intestinal fat absorption. By resorting to specific antibiotic therapy, the investigators were able to bring about a striking improvement in fat absorption in these patients, and a significant improvement in nutritional status and body weight, coincidental with a return of the intestinal bacterial flora to normal.

A number of new practical clinical and surgical techniques have been developed by Institute grantees at the University of Minnesota. One of these new procedures achieves the relief of intestinal distention without the need of surgical intervention. Here grantees overcame the difficulty, which has plagued clinicians in the past, of passing a long intestinal tube from the stomach well into the distal reaches of the intestine, by developing a new type of plastic tube reinforced with a coiled spring innerlining. With the help of this new instrument the grantees were able to achieve decompression of the distended and obstructed bowel in 32 patients with intestinal obstruction in whom otherwise surgical intervention and the performance of an external drainage vent would have been necessary.

An additional procedure has been worked out which permits the detection of a strangulated intestinal obstruction, a condition which calls for immediate surgical correction. The newly developed procedure involves visualization of the entire arterial supply of the bowel under X-ray with the aid of an injected radio-opaque dye. When a strangulated obstruction is present, vascular occlusion in the major portion of the vessel is detected by a filling defect and the fine radicles of the arterioles which enter the bowel wall do not show up very distinctly.

DISEASES OF METABOLISM

In view of the interest shown by the committee in the subject I shall devote the bulk of my testimony in the field of metabolic diseases to cystic fibrosis. I would like to emphasize, however, that National Institute of Arthritis and Metabolic Diseases scientists and Institute grantees who are occupied with very extensive research efforts related to a large number and variety of metabolic diseases have again proven gratifyingly productive in this area which is replete with a multitude of challenging problems. As an example of this productivity I shall briefly mention one specific achievement, primarily because of its unique nature.

The term "porphyria" embraces a group of diseases in which symptoms involving the skin, abdominal organs or the nervous system are associated with the urinary excretion of a variety of abnormal forms of porphyrin (breakdown products of the essential red blood cell pigment, hemoglobin). Heretofore, porphyria has been regarded as an inborn error of metabolism, based on an inherited constitutional defect. Recently an outbreak of several thousand cases of cutaneous porphyria occurred in Turkey.

The afflicted patients were obviously not genetically related—they included several distinct ethnic lines (Kurds, domestic Turks, and Turks repatriated from the Balkans after centuries of residence there.) The dietary histories suggested that virtually all patients had consumed wheat which had been accidentally contaminated with a fungicide, hexachlorobenzene, but this alone was not considered conclusive etiologic proof, especially since porphyria was presumably an exclusively hereditary disorder. In a well-organized study involving laboratory animals, two Institute grantees at Harvard University Medical School demonstrated that inclusion of hexachlorobenzene in the diet can produce the signs and symptoms of porphyria. With small quantities the process was reversible in some cases, the symptoms disappearing after deletion of the fungicide. However, repeated feedings resulted in a typical irreversible porphyric state with liver damage, neurologic complications, and the urinary excretion of a variety of porphyrins. This study represents the first convincing evidence that porphyria may be an acquired disease and not exclusively an hereditary disorder; simultaneously it contributed important practical knowledge in the field of insecticide and food toxicology.

Cystic fibrosis

Significant strides have been made in the research attack on cystic fibrosis by both Institute scientists and grantees. Additional evidence has been produced in Bethesda that the disease is not limited to infants and young children but that, depending on the extent of the genetic endowment in the individual, the disorder may express itself through only partial manifestations of its symptomatology. Individuals with an incomplete hereditary load (heterozygotes) may thus survive into adulthood and many adult patients with chronic pulmonary symptoms, chronic digestive tract symptoms, or both, may be true, though partial, cases of cystic fibrosis. Institute scientists have succeeded in finding a significant number of such cases with the aid of the iontophoretic sweat test, and extensive work is being carried out for further clarification of this concept of adult cystic fibrosis. Extensive, similar work is being carried out by grantees at Ohio State University and at San Diego State College.

In an intensive collaborative study with a grantee at Columbia University a gummy substance, an abnormal mucopolysaccharide fraction presumed to lend the special viscous nature to the pathologic mucus secretions in this disease, has been isolated from the duodenal contents of cystic fibrosis patients, and its chemical characteristics are now being investigated. In similar studies, abnormal viscous glycoproteins have been isolated in the urine of fibrocystic patients, and the chemical characteristics of these substances have been partially determined. The biosynthesis of abnormal mucopolysaccharides (of the type responsible for the viscidity of mucus in cystic fibrosis) is being investigated with the aid of a natural model for mucus formation, the hen oviduct. So far, hitherto unknown sugar nucleotides have been isolated which are suspected of being active precursors of natural polysaccharide mucus components. With the aid of this newly unfolding biosynthetic system it is hoped that it will be possible to define biochemically and to elucidate stepwise the process of normal, and eventually abnormal, mucus formation.

Concurrent with such fundamental investigations which lay the foundation for major future advances in cystic fibrosis, work along applied lines is being carried out and has produced a number of significant advances in the clinical management of cystic fibrosis patients.

During the past year, an Institute grantee at the University of Pennsylvania has developed a new method of inhalation therapy which involves the use during the patient's sleep of liquid aerosols containing 3 percent sodium chloride. Preliminary trials with 24 patients have demonstrated a gratifying increase in bronchopulmonary drainage in patients thus treated due to the enhanced dispersion of the viscous fibrocystic pulmonary secretions in the resulting local saline medium.

The same investigator is also evaluating the use of a newly developed percussion vibrator which has shown promise for enhanced bronchial drainage of the inspissated, almost immovable, fibrocystic pulmonary secretions.

Concomitantly with the encouraging studies on the efficacy of the recently developed synthetic penicillin Staphcillin by the National Institute of Allergy and Infectious Diseases, this antibiotic has been evaluated in our patients in Bethesda and has been found strikingly effective, administered either by injection or inhalation, against drug resistant pulmonary staphylococcal infections.

Since the pulmonary involvement dominates the clinical picture in cystic fibrosis and ultimately determines the fate of the patient, the performance of this new antibiotic is highly encouraging. Also during the past year, trials with the new antibiotic colymycin have given encouraging results in those of our patients with *Pseudomonas aeruginosa* infections of the respiratory tract, which ordinarily do not respond to conventional therapy.

We are expending considerable efforts in the elaboration of simple diagnostic methods which could be widely used by physicians and hospitals without elaborate laboratory and clinical facilities. During the past year we have succeeded in devising and perfecting a relatively simple but exceedingly accurate test which measures the degree of intestinal fat absorption in cystic fibrosis patients; impairment of intestinal absorption of dietary fat is a prime symptom of involvement of the pancreas. This test employs the administration by mouth of lipiodol, a substance consisting of an iodinated fat which is ordinarily used in radiography and which is readily and inexpensively obtainable in all pharmacies. The simple test is based on determination of the urinary iodine which has been split off the fats which were absorbed from the intestinal tract. Combined with determination of fecal fat on 4-day balances, this test achieves hitherto unobtained accuracy in the evaluation of intestinal fat absorption in cystic fibrosis patients.

We have taken steps to transmit information on new findings of our scientists and grantees to practicing physicians so that the advantages will accrue to cystic fibrosis patients at the earliest possible moment. In order to acquaint clinicians and research workers throughout the country with our latest findings, we have prepared a comprehensive scientific exhibit on the disease, detailed directions on the iontophoretic sweat test, and literature concerning the most recent and most effective methods of treatment. We have brought these to the attention of literally thousands of physicians at recent medical meetings and have met an encouraging interested response from these men who are apt to meet cystic fibrosis in their practice and feel a need for the latest practical information.

NONCLINICAL RESEARCH

Underlying all the fields of biology and medicine is a substructure of fundamental knowledge common to all the preclinical and clinical sciences. Obtaining this basic knowledge, without which progress in clinical research is difficult, is one of the prime activities of the National Institute of Arthritis and Metabolic Diseases. This year I am pleased to communicate to the committee from among the very extensive array of highly productive achievements in the fundamental sciences, the results of the work of two of our scientists in Bethesda, Drs. Nirenberg and Matthaei, who have been successful in the partial cracking of what is considered the most important code in biology, the message code of heredity, specific for each type of living organism. This code system involves the hereditary materials DNA (deoxyribonucleic acid) and RNA (ribonucleic acid), which occur in all living cells. DNA's ability to transmit genetic instructions from one generation to the next derives from its chemical configuration which makes up a template or mold. This template of hereditary specifications is transferred by "messenger" RNA which, in turn, directs the manufacture of protein needed for life. RNA's job as a biochemical middleman is dependent on the configuration of four components, organic bases, in its molecular structure. The sequence of these 4 bases determines how 20 different amino acids in the metabolic pool of a growing cell will be linked to form specific protein molecules.

Drs. Nirenberg and Matthaei prepared a protein synthesizing system using bacterial cell extracts. The biological pilot plant was capable of converting amino acids fed into it into random protein molecules. By also feeding into the system samples of a specially synthesized RNA, they were able to direct the process to produce protein material incorporating only one of all the available amino acids. Similarly, when other synthetic RNA messenger compounds were used, which contained a predetermined different configuration and sequence of base components, different amino acids were incorporated into the protein produced by this system. Thus, when the structure, or code, of the messenger RNA was known, it was possible to relate the code to the specific nature of the protein produced in the simulated "growing cell material." This work represents the first experimental evidence which permits direct translation of the RNA code and its role in protein synthesis.

In this necessarily limited narrative, it is impossible to do justice to the very numerous achievements of our scientists and grantees in the area of basic research. I will merely mention two other examples of the type of findings obtained, which pave the way for future progress in clinical research.

Institute grantees at the University of Michigan have succeeded in clarifying a major mechanism through which the pituitary growth hormone mediates its known growth-stimulating action. Using a synthetic "unnatural amino acid which is not metabolized by the cells, but which is transported in the body of experimental animals in a manner similar to naturally occurring amino acids, these investigators demonstrated that growth hormone specifically stimulates the transport of amino acids into cells from the surrounding serum—the essential first step in the intracellular synthesis of protein.

Another study in our Bethesda laboratories established that the principle of enzymatic adaptation, well-documented in bacteria, holds true in mammals as well. The investigator was able to demonstrate that when the diet of experimental animals was changed radically to include a very high percentage of protein, the livers of the animals adapted to the unusual metabolic load by increasing the total amount of amino nitrogen-disposing, urea-synthesizing enzymes. This adaptation proceeded along quantitative lines; a fourfold increase in dietary protein load resulted in a fourfold growth in the enzymes investigated.

Before concluding the narrative on basic research activities, I would like to add that during the past year a number of investigations were started concerning the metabolism of skin in health and disease—an essential subject about which very little reliable information exists.

INTERNATIONAL CIVILIAN NUTRITION ACTIVITIES

In previous years I have apprised the committee of our participation in the nutrition survey activities of the Interdepartmental Committee on Nutrition for National Defense (ICNND). Up to last year, surveys had been conducted in 14 countries in Asia, Africa, and South America. Since then, extensive nutrition surveys were conducted in the Lesser Antilles, Caribbean Islands, Lebanon, the Republic of Vietnam, Thailand, and Burma. In contrast to the early surveys conducted, which were oriented primarily toward the defense forces of the respective countries, considerable emphasis was placed on the nutritional status and nutritional needs of the civilian population in the areas surveyed where malnutrition has economic as well as health implications.

We have found our international nutrition activities are of value not only to the countries served, but they have become increasingly valuable to the National Institutes of Health and other participating institutions in the field of public health and medical research. Direct benefits not only accrue through the training of personnel in clinical nutrition, but in addition, our Institute has been able to extend markedly its knowledge of nutritional diseases associated with the dietary deficiencies prevalent in the populations studied.

CLINICAL RESEARCH CENTERS

During the past year this Institute has begun to support a small number of highly specialized clinical units as resources for performance of superior clinical research in metabolism and the rheumatic diseases. Preliminary reports indicate that these small, specialized units are fulfilling effectively a need not met by other clinical center programs. Thus, although this Institute philosophically supports wholeheartedly the concept and program of the General (multicategorical) Clinical Research Centers and believes that clinical research is very valuably enhanced in quality on a broad basis by this system, we see a limited but specific additional need for support of clinical research facilities within some of our fields of special interest. In certain institutions within which there is a major research effort in arthritis, diabetes, or other areas of our particular research concern, which in that institution by tradition and development outweighs extensively efforts on behalf of other diseases, significant value is visualized in the organization of discrete, highly organized nursing units or wards to provide the environment required for high level, well-controlled clinical research.

Examples of such a useful facility are one for the conduct of careful clinical studies of carbohydrate and fat metabolism with respect to the mechanism of action of insulin and of the oral drugs in diabetes mellitus, and one for study of protein and polysaccharide metabolism in the rheumatic diseases. In view of the type of investigation conducted on patients with the diseases of our interest, these units are being arranged for superior performance of metabolic studies: ordinarily these special clinical research units are of a size of 4 to 12 beds, are supported in close proximity by pertinent laboratories, diet kitchens, etc., and are manned by well-trained nursing and technical personnel, characteristic of the highest level metabolic and clinical research wards already in existence. Clinical research centers of this specialized type and generally limited size do not displace or supplant research project activity, but rather provide the physical and staff facility to give the most meaningful support, by way of a highly controlled environment, to metabolic and rheumatic disease research.

TRAINING FOR MEDICAL RESEARCH

My report to the committee to this point has been concerned primarily with the activities and scientific accomplishments of our laboratories at Bethesda and of scientists supported by research projects grants of this Institute. I wish now to describe briefly another important place of support: training for careers in academic medicine, primarily for research, by training grants and fellowships.

This program was designed to provide a gradually expanding force of trained investigators to intensify research efforts upon the various diseases within our area of interest and to improve the use of fundamental biochemical and physiological knowledge in applied clinical accomplishment. We have continually been assessing the success of this program by means of the very high percentage of men who have become sufficiently well trained under this program to compete successfully for research grant funds. At present we are engaged in a more intensive study of the value of National Institute of Arthritis and Metabolic Diseases training grants, primarily in clinical research. Although this evaluation is not complete, it has progressed far enough to indicate that training grant programs have had a very marked strengthening influence on the caliber of clinical investigation, with consequent great dividends to the American people in improved health from clinical research accomplishments. National Institute of Arthritis and Metabolic Diseases training grants have clearly been responsible for the considerable vitalization of arthritis research to its present point of intense efforts to relate bizarre immunologic reactions to the cause of this disease; it is to be reasonably expected that other fields of our interest, for example, gastroenterology, will soon be showing the effects of the improvement in caliber of manpower devoted to research, resulting in definite measure from increased training grant support. The effects of training and fellowship funds, although less direct than research project support, ultimately bring about substantial and valuable research endeavor with subsequent benefits to the national health.

PROGRAM NOTES

The limited scope of this narrative does not permit mention of all of the productive achievements of the past year in areas not covered in detail in this testimony. These include advances in hematology, familial diseases, orthopedic surgery, radiation protection, obesity, endocrinology, nutrition, and many others.

This Institute feels that it carries a serious obligation to communicate, at the earliest possible moment, information concerning discoveries of the scientific staff and of Institute grantees to the practicing medical community. We have, therefore, made marked efforts in this direction during the past year. These include the preparation of a considerable number of comprehensive scientific exhibits on the latest advances in specific problems and diseases as well as similar pertinent literature. These have been brought to the attention of many thousands of physicians at scientific and medical meetings, and postgraduate educational events. A gratifying response has occurred in the form of inquiries from interested physicians who see these disorders in their everyday practice. Moreover, to facilitate a rapid interchange of the latest scientific specialized information and to aid in cross-fertilization of ideas and scientific approaches, this Institute has encouraged relatively small working meetings and conferences of scientists from disciplines within its area of responsibility.

CONCLUSION

The past year has witnessed significant advances and productive research accomplishments in the various areas of responsibility of the Institute. New discoveries and valuable improvements have enriched the armamentarium against the diseases in which this Institute has special responsibilities. Simultaneously, the frontiers of basic biological knowledge have been pushed forward, broadening the common foundation of future progress in clinical research and the art of healing. We hope that in the years ahead this balanced advance in fundamental knowledge and applied study will continue to spell benefit to our untiring progress in the battle against disease and disability.

In conclusion, Mr. Chairman, the request for 1963 is $91,921,000 which will provide for an estimated 353 additional research projects in arthritis, diabetes, gastroenterology, and various metabolic diseases.

This request for 1963 is distributed among program activities as follows:

Grants and related contracts:	
Research	$68, 754, 000
Fellowships	1, 177, 000
Training	9, 525, 000
Subtotal, grants	79, 456, 000
Direct operations:	
Research	10, 173, 000
Collaborative studies	650, 000
Review and approval of grants	1, 337, 000
Administration	305, 000
Subtotal, direct operations	12, 465, 000
Total appropriation request	91, 921, 000

RESEARCH ADVANCES

Dr. Daft. Among the many advances we have submitted in the opening statement, there are three particular ones which I should like to discuss in a little more detail, very briefly, if I may. One of these is in the field of rheumatic diseases revolving particularly around the rheumatoid factor, which has been discussed with the committee on previous occasions. This factor is of great help to us in the diagnosis of patients and also is very important in giving us more light on the rheumatic diseases, particularly on rheumatoid arthritis, and it gives us real hope that we are finding the cause of rheumatoid arthritis. The second advance is in the field of the typing of platelets, a substance in the blood. The platelets are very important for preventing hemorrhages. They have to do with blood clotting and prevent uncontrolled hemorrhages. The third is in the area of basic science and is the breaking of the genetic code.

RHEUMATOID FACTOR

Going back to the first of these, the advance with regard to the rheumatoid factor—the rheumatoid factor is a protein of high molecular weight which occurs in the blood of most patients with rheumatoid arthritis. There is a number of methods for determining this factor, its presence and also its level in the blood.

On previous occasions we have discussed this very largely as a diagnostic factor. When there is any doubt as to the diagnosis of rheumatoid arthritis, this has been a great help to us in confirming that diagnosis.

During the past year work on this factor has been extended considerably to the point where it is of great help to us in knowing what the progress of the disease will be in individuals. This depends on the level as well as the presence of the rheumatoid factor in the blood.

A study by one of the Institute scientists in collaboration with a group in England has shown that you can divide patients with beginning rheumatoid arthritis into two groups—those where the factor is missing from the blood, or where it is in very low levels, and those who have a high level of the rheumatoid factor in the blood.

In the first group the disease does not progress with the same bone and tissue destruction as it does in the latter group. Therefore, by separating patients into these two groups the physician is helped a great deal in knowing how to treat them.

Mr. Fogarty. How can this be determined and at what age?

Dr. Daft. At any age that the disease is present.

In the general population of all ages this factor is missing. It has been found that it does occur in some percentage of the relatives, the close relatives of patients with rheumatoid arthritis. Therefore we know that the disease has somewhat of a genetic control.

Mr. Fogarty. So it would be well for the relatives of people who have this disease to be examined?

Dr. Daft. Yes, sir.

In patients with the disease, which occurs at all ages, the level of this factor in the blood is of great importance in determining what the course of the disease will be. If the factor is at a low level, or if it is absent, you can start with very mild treatment, merely aspirin and physical therapy, and expect to control the disease with this therapy.

Those patients with a high level in the blood are much more likely to develop a serious disease and must be watched more carefully.

It will probably be necessary in many of these patients to use cortico-steroids to control the disease, either cortisone or the newer derivatives of cortisone, prednisone, and other newer derivatives.

NEW DRUGS FOR TREATING RHEUMATIC DISEASES

Mr. Fogarty. Are there any new ones since you appeared last year?

Dr. Daft. I have been hearing, sir, there will be announced soon some new drugs which will have some value over existing drugs. There have been no announcements of any particular ones at the present time, but there is a great deal of work going on in this area. I am certain that we are going to develop a family of drugs, some of them better for one patient, one of them better for a certain group of patients, I should say.

Mr. Fogarty. Are these being developed at the various pharmaceutical houses?

Dr. Daft. These are developed almost entirely by the pharmaceutical houses, and then are being tested both at the National Institutes of Health and throughout the country in the medical schools. Of course, a great deal of testing must go into this before they are ready for general use, so we are certain there are no serious side effects.

Mr. Fogarty. Do you think there are some that show real promise?

Dr. Daft. Yes, sir. The testing on these is in the early phases at the present time. No announcements have been made, but I am certain there are some being developed that have considerable promise.

Mr. Fogarty. When do you expect some announcements might be made?

Dr. Daft. Within the next few months.

CAUSATION OF RHEUMATOID ARTHRITIS

A very important part of the study of the rheumatoid factor has centered around its significance in the causation of rheumatoid arthritis. Here we are making very real progress. There is a very real hope that we are on the right track and will understand through the study of the rheumatoid factor the precise cause of rheumatoid arthritis.

This is a large protein which exists in the blood of most patients with rheumatoid arthritis, which has most or probably all of the characteristics of an antibody. In other words, this has been formed in the blood as a result of there being an antigen which called forth this particular antibody.

Mr. Fogarty. Called what?

Dr. Daft. Some material which sensitizes the individual and calls forth this immunological response, just as the toxins of bacteria stimulate the manufacture of antibodies which help to combat the disease.

There are some side effects, however, in the antigen-antibody reaction which are not always to the good of the patient, even though this is a defense mechanism. In this particular case, it appears that this is not a normal reaction to antigens that are normal or else that there are antigens in these patients which are abnormal.

The recent progress indicates that in certain people there exists in the gamma globulins, which is one fraction of the blood, a substance which calls forth this response. This is of great help in understanding what is going on here. We have identified, at least partially, these offending substances, this offending substance, which calls forth in rheumatoid factor in the blood. It does not get us to the point yet of knowing for certain that this is the cause of rheumatoid arthritis. It may be something which is going on at the same time. But it seems more and more certain that rheumatoid arthritis as a disease is related very closely to this phenomenon which leads to the rheumatoid factor in the blood.

I think we are making very good progress through the study of this factor in understanding rheumatoid arthritis. I hope it can be reported to you in subsequent years that we will know the cause and then hopefully we will know how to control the cause.

Mr. Fogarty. Is it going to take years to find this? I was hoping we might be able to step up this program and find the answer a lot sooner.

Dr. Daft. All of us hope very much, of course, that this will proceed much more rapidly than it does, but despite the fact that about 40 percent of all of our support in the area of rheumatic diseases is in the study of the rheumatoid factor, the progress still is admittedly much slower than any of us would like.

Mr. Fogarty. Are you more optimistic this year than the last 4 or 5 years you have been before us?

Dr. Daft. Yes, sir. We feel certain we are nearer the solution.

Mr, Fogarty. Is there anything we can do now to help you develop this program? Are there any other programs you would like to see developed if you had the funds?

EMPHASIS ON SENSITIVITY-ALLERGIC PHENOMENA

Dr. Daft. I cannot point to any one specific study that is not being made which I think will solve this problem. We are putting a great deal of our resources into this. It is one of these things where the basic knowledge is not yet sufficiently helpful to give us very rapid progress. I think we will have to put greater emphasis into a basic understanding of the sensitivity-allergic phenomena which apparently underlie the production of this factor in the rheumatic patients. That is going on, and we are emphasizing it more and more.

Mr. Fogarty. What do you mean in my language?

Dr. Daft. I should say that we are not denying very much in the way of support to people who are working in this area. It is of so much importance.

Mr. Fogarty. I understand that, but I thought you said you have to put more emphasis on what?

Dr. Daft. We do not know enough about this general body reaction, the antigen-antibody reaction, particularly in the area where it is abnormal.

Mr. Fogarty. What do you mean by antigen-antibody reaction?

Dr. Daft. This is a phenomenon which underlies all defenses against disease and also sensitivity reactions. That is, it is the production of antibodies against disease which is an important method of combating disease. Part of this is done purposefully in the individual by immunization with either killed virus or killed bacteria; live virus or live bacteria are also used to stimulate defenses against all sorts of diseases.

There is also the area where there are somwhat abnormal reactions, and we do not understand well enough yet the basic phenomena of the so-called abnormal reactions. We must know exactly how an individual responds to all foreign substances coming in, why it leads in one case to a protective substance, why it leads in another case to allergies, for example.

In this particular area we are setting up in our clinical department a study of this type of reaction which we hope, of course, will help us to solve this particular problem.

REDUCTION IN ORIGINAL REQUEST

Mr. Fogarty. You were cut about $12 million from what you asked for, I believe.

Dr. Daft. Yes, sir; that is correct. Perhaps I might express it this way. This is a very important area. We are going to support this even at the expense of some other things. So I cannot truthfully say that——

Mr. Fogarty. Suppose you did not have to take it away from other areas. How much do you think you could use to advantage in addition to what you have planned for 1963? You think this is a real important area in this overall program now.

Dr. Daft. I should be very happy to submit that for the record, if I may.

Mr. Fogarty. All right.

(The information follows:)

Program appraisal reveals that an additional $2 million could be wisely invested in rheumatoid factor studies.

AREAS IN RHEUMATIC FIELD NEEDING MORE ATTENTION

Mr. Fogarty. What other areas in the rheumatic field do you think need more attention?

Dr. Daft. Mr. Fogarty, there are a number of areas of research which should go forward at the same time as the program on the rheumatoid factor. I think that at the moment this is the most important lead we have. I am very happy to see a very large part of our resources of manpower, space, and everything else put into this program.

We cannot at the same time neglect other possibilities. We cannot neglect the possibility that a virus is involved. We cannot neglect the possibility that bacteria may be in some way involved.

I might say in this connection that one of our grantees has injected into animals a sterile material which helps to enhance the antibody response to any injected foreign material.

Mr. Fogarty. Just one moment off the record.

(Discussion off the record.)

Mr. Fogarty. Proceed, Doctor.

Dr. Daft. I had mentioned that an investigator, who is a grantee of ours, is producing arthritis in rats by injecting sterile material which seems to enhance the type of reaction which we suspect to underlie rheumatoid arthritis. This again is a type of investigation which must be followed, and it must be discovered for certain whether there is any virus involved or any bacteria involved. If a bacterium should be involved, as in rheumatic heart disease, where an early infection leads later to the sensitivity reaction which shows up in rheumatic heart disease, this would be of tremendous importance in controlling the disease, whenever a person got the infection with that particular organism.

These are general areas in which we must carry on studies at the same time that we are studying the rheumatoid factor, its help to us in the care of patients, its importance in understanding the actual causation of rheumatoid disease and, hopefully, of course, its cure.

BLOOD PLATELETS RESEARCH

I would like to mention very briefly a recent discovery in the area of blood platelets. A method which is used to determine the type of red blood cell and other factors in the blood is a particular technique called agglutination, that is, a "grouping together." The red blood cells clump together and fall out in this particular test.

This method has been tried for identification of platelets, but it does not work; it is not sensitive enough. But very recently one of our investigators at the Institute has shown that he can use another technique. I will give the name, without describing it too carefully. It is complement fixation. It is a more laborious and more involved technique, but by the use of this he has been able to show that there are different types of platelets. He has shown at the present time there are seven different types, and there are undoubtedly a few more, although the seven cover most of the population group.

This is of immediate importance in several clinical areas, one being in what is called neonatal purpura, which merely means the newborn baby has a bleeding phenomenon, that it bleeds into the skin where it is very visible and into some other places. Some of these infants are in very serious condition.

Also there is a new technique for the transfer of platelets from one individual to another, to increase the concentration of the platelets in situations where bleeding might be a problem. This is called platelet transfusion and is used particularly in aplastic anemia and leukemia. In leukemia, doctors will give drugs to depress all of the blood forming elements in order to depress particularly the excess formation of white cells, which is the difficulty. In these patients, usually children, who are treated in this fashion, the drug treatment may depress the already low platelets in the blood so that there is a tendency for bleeding.

For these cases, platelet transfusion is usually recommended, but in some instances after a few transfusions, it no longer works.

It has been demonstrated by an Institute investigator that the reason for such failure is that the individual has become sensitive to certain platelets. The individual has developed an antibody to them. Therefore, when this particular type of platelet is put in, they are destroyed by the antibody. By this new typing technique physicians can now put in platelets of a type to which there will be no reaction of this sort. Therefore, the platelets are not destroyed, and one can continue transfusions successfully over the period necessary.

In the case of the infant with bleeding, a reaction between platelets and antibody is also the cause. The type of platelet is inherited. It is genetically controlled. If an infant, before birth, develops a different type of platelet than its mother, this would be inherited from the father. Then this platelet may accidentally get into the mother's bloodstream and produce an antibody; since it is a foreign platelet to the mother, the antibody goes back into the infant, destroys the infant's platelets and causes bleeding. You control this over the first couple of weeks of life, and then you are perfectly safe.

Just how this new discovery will affect the treatment of neonatal purpura is not absolutely clear, but it seems that we will be able to use the right type of platelet to get the infant over this very short crisis.

BREAKING THE GENETIC CODE

The third advance I would like to mention very briefly is a little more difficult, but it is one of extreme importance. This is in the breaking of the genetic code. We have discussed before the committee on previous occasions the way in which genetic information is transmitted from one generation to the next. Now we might take two cases. One is when there is an injury to the body, to one part of the body. If this injury is not too severe, the body repairs it. It always repairs it with the same type of cell that was destroyed. If you have a cut on the skin, the type of material there which is replaced is normal skin tissue. If you lose part of the liver, the liver repairs itself, but always with liver cells, which differ a great deal from skin cells.

We have known for some time that there must be in the cells the information which permitted them to make the right kind of cell. A little bit more complicated case, of course, is the fertilized egg.

One fertilized egg will grow into a chicken, another into a mouse, another into a human. There has to be something in these cells to tell the other cells exactly how to develop the type of material that it must manufacture.

In recent years it has become more and more clear that this information resides in the nucleic acids in some way which was not understood. We had an idea, a considerable idea, as to how this might work. Our scientists have concentrated on one aspect of this, but a very important aspect. That is in the manufacture of proteins. The proteins are extremely important for several reasons. One is that they are the building blocks for cells, but another, the proteins include all of the enzymes. Here, of course, we get into the diseases of childhood such as galactosemia, cystic fibrosis, and others, because in these diseases there is a defective protein which is manufactured in some way.

What we have found out is a method of making in the test tube some nucleic acids, not the ones yet which exist in the body and determine this particular process, but simple ones at first. They have building blocks. In the nucleic acids there are only four building blocks, four types of material which build up the nucleic acids. It is only because we have a very large molecule with many different combinations of these blocks that they can do all of the things that are necessary.

The first start was to take one of these building blocks and make a nucleic acid entirely out of that. That was a substance called uridylic acid. The investigator made what he called polyuridylic acid, which meant that this nucelic acid was made up of only one building block, which we will call A, and it was A, A, A, A magnified thousands of times. This one nucleic acid was found to be responsible for putting into the protein molecule one specific amino acid and only one, which is phenylalanine. Now they have gone much further than that and have shown that certain combinations of these four building blocks—A, B, C, and D—are responsible for other parts of the protein. Hopefully, we can look forward—I will admit this is dreaming a little bit, looking into the future—it will require a very great deal of work, of course—finding out the actual structure of the nucleic acids in the body which do determine what enzymes, what proteins are made by that particular organism, what is made in the human and what should be made, and what sometimes is not.

Then after we have done that, which is very laborious and, we must admit, will take a long time, then hopefully we shall get to the point where we can in some way modify protein synthesis when it is defective or actually supply the missing nucleic acid to the cells.

GALACTOSEMIA

For example, in galactosemia, where we know one certain nucleic acid is wrong in the cell of the child with galactosemia——

Mr. Fogarty. What is that?

Dr. Daft. It fails to manufacture one specific enzyme. This particular enzyme—we do not know the exact nature of the nucleic acid yet which determines the fact that this one enzyme is completely lacking. In this case it is not a defective enzyme, it is a completely lacking enzyme.

Therefore, in breaking down the sugar of milk there is one step which does not happen. You get piling up in the body a derivative of that sugar which is poisonous to the infant and causes death in many cases, and when the infant survives, it causes blindness and imbecility.

Mr. FOGARTY. When it causes death, what is the reason for death?

Dr. DAFT. The reason for death is the piling up of a normal sugar derivative in the body. In this particular case galactose is one-half of the molecule of the sugar in milk. The other half is glucose. The body metabolizes the glucose in the disease but the other half of the molecule it does not. What it should do and does in normal individuals is change galactose over to glucose. This goes through three steps. There are three enzymes involved in this transformation of the one sugar to another. Two of those enzymes are still present normally in this youngster, but unfortunately the third one is completely lacking. This defect exists in the liver; it also is in red cells. We can make a test for that, as I believe I have discussed with you before, by taking just a little blood, even placental blood, and testing for the presence of this specific enzyme.

Now we are quite sure that this enzyme is lacking because the cells lack this nucleic acid, because if the right nucleic acid, the structure of which we do not know yet, were present in these liver cells, it would make this enzyme and the child would be normal.

Mr. FOGARTY. How many children die of this per year?

Dr. DAFT. Galactosemia is one of the rare diseases, fortunately. The exact number in the country we do not know.

Mr. FOGARTY. Why do we not find out?

Dr. DAFT. That is being done to a certain extent. It has proved more difficult than we had anticipated in getting a little testing kit which every doctor could use or which could be used in the hospitals. Hopefully, we will have such a kit in the near future, which can go particularly into lying-in hospitals. The obstetrician can preserve the placenta, and if the child develops diarrhea for any unexplained reason, you can immediately test then for whether or not galactosemia is the cause of the diarrhea, and all you have to do then is take the child off milk and he develops quite normally. So, testing will be done. Finding out exactly what the incidence is will be really a byproduct; the important thing, of course, will be to identify the individuals with this disease and save their lives, but we will also find out exactly how common it is at the same time.

CYSTIC FIBROSIS

As you know, there are a number of other diseases which are similar in one way or another which are hereditary. One of them that I know you are very interested in is cystic fibrosis. Hopefully, we can find out also what is the precise defect in cystic fibrosis in exactly the same way. We are making progress, but we do not know yet the precise lacking substances in cystic fibrosis.

Mr. FOGARTY. What do you mean by progress?

Dr. DAFT. The progress in the field of cystic fibrosis has been in two areas. One has been in the management of the patients. Investigators are developing methods of preventing death of the patient and also allowing him to live more comfortably. This is an area, I should say, which is the responsibility of two institutes, as you remember, the Allergy and Infectious Diseases Institute, and our own responsibility for the metabolic aspects. I know Dr. Andrews will tell you something of the fact that they are better able to control infection in these patients, and infection, after all, is what kills the patient eventually.

There is also progress from one of our grantees in a very practical matter, which is loosening the mucus. One of the organs involved is the lungs. You get an abnormally viscous thick mucus there, which is why the bacteria grow so well, and eventually they become unmanageable.

There is now a very practical therapy of inhalations while the patient sleeps, which loosens the mucus. Also doctors are using some ultrasonic vibration in loosening it. So the patient is more comfortable; there is less danger of developing a fatal infection.

We are progressing slowly again, I am sorry to say, in our understanding of the disease. There is a lot of basic research going on in this area. It is one of those things, as in many other areas, such as cancer, where we are having difficulty in pinpointing the precise abnormality. But we are learning more about it each year. Each step that I could report is small in itself, but there is progress being made in our understanding of exactly what is happening in the body, what the defects are in the concentration of salt in the sweat, for example, the fact that these patients concentrate a higher amount of salt and lose it from the body by that mechanism, and all of the other aspects of the disease—slowly we are learning more about them, but we have not learned about the cause.

I might mention, sir, we have a special report on cystic fibrosis prepared by the two institutes.

Mr. FOGARTY. Put that in the record.

Dr. DAFT. Yes, sir.

(The information follows:)

SPECIAL REPORT: CYSTIC FIBROSIS

Cystic fibrosis is the most frequent, fatal hereditary disease of children. As a cause of death in children it outweighs such well-known diseases as rheumatic fever, diabetes, and poliomyelitis. Although cystic fibrosis (CF) has been recognized as a separate disease only within the last 25 years, it is now diagnosed with increasing frequency throughout the world. In the United States it is estimated that anywhere from 2 to 20 percent of the population may be genetic carriers of the disease, and about 1 infant out of every 1,000 births is afflicted.

Cystic fibrosis affects the exocrine glands—glands which discharge their secretions onto the skin (sweat glands) or into organs which connect to the outside of the body (lungs, intestines, etc.), either directly or through special ducts. In cystic fibrosis, the mucus-producing glands fail to secrete their normal, clear, free-flowing fluid. Instead, they produce an abnormal, thick, sticky mucus which tends to obstruct the ducts or openings of the glands. When the thick mucus accumulates in the ducts of an important gland such as the pancreas, it interferes with its function to supply much-needed digestive enzymes to the intestinal tract.

Another basic abnormality is found in the nonmucus secreting sweat, salivary, and tear glands. In cystic fibrosis, the secretions of these glands usually contain an excessive amount of salt. Because of the sweating defect, many cystic fibrosis patients are unable to conserve salt, especially in hot weather, and this condition may be severe enough to lead to death.

Almost all patients develop chronic lung disease at some time during the course of their illness. Thick mucus deposits tend to clog passages in the lung or branches of the windpipe, causing obstructions manifested by labored breathing or a chronic cough. As time goes by, bacterial infections set in and the child may develop chronic bronchitis. The patient is usually extremely susceptible to lung infections and may succumb to pneumonia. The obstructed, damaged lung tissue may also serve to impede blood circulation and occasionally a child may die of chronic heart strain.

Cystic fibrosis is not an infectious condition which can be acquired from others or transmitted directly to them since the disease is inherited from parents who carry the genetic trait for the disorder from generation to generation. A carrier of the trait may not show any symptoms of the disease, yet he is capable of passing the trait to his offspring, who in turn may have inherited a partial manifestation of the disease. When both parents are carriers, their offspring have a chance of being born with cystic fibrosis.

Recent statistics show that among children in the United States cystic fibrosis accounts for virtually all cases of pancreatic deficiencies, and for a great majority of chronic (nontuberculous) lung diseases and for many liver diseases. Although labeled primarily as a disease of young children, improved diagnostic methods have provided evidence of an increasing frequency of cystic fibrosis among older adolescents; also, there is now evidence that some adults with chronic lung disease may belong in the cystic fibrosis disease category.

Research on cystic fibrosis at the National Institutes of Health is the joint responsibility of two Institutes, the National Institute of Arthritis and Metabolic Diseases (NIAMD) and the National Institute of Allergy and Infectious Diseases (NIAID). Both are conducting studies in their own facilities at Bethesda, Md., while also supporting investigations elsewhere under research grant programs.

NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES

Significant strides have been made against cystic fibrosis both by Institute scientists in Bethesda and in the more than 30 active research projects supported by the Institute. Much of this research deals with attempts to seek out and discover the basic defect in cystic fibrosis, as well as to study the genetic aspects of the disease.

In genetic studies, additional evidence has been produced indicating that the disease is not limited to infants and young children but that, depending on the extent of the genetic endowment in the individual, the disorder may express itself through only partial symptoms in adults. Studies of the hereditary transmission of the disease by grantees have also uncovered specific antibodies against pancreatic tissue in the blood of 28 of 32 children with cystic fibrosis. Attempts are now being made to find what antigens are provoking these antibodies, and whether or not relatives of these children also have similar antibodies.

The development of an instrument by Institute scientists to measure simultaneously the rate of sweating and the functional activity of sweat salt has provided some interesting and potentially important information on the mechanism of sweating of the cystic patient. Preliminary data obtained from using this device on a small group of patients with cystic fibrosis suggest that the relative inability of sweat gland tubules to reabsorb and return "sweated" salt to the body is not due to a defect in the tubules themselves but to the formation of an abnormally concentrated precursor solution released originally in the acinar "root" portion of the gland. The finding of the exact defect in this mechanism might reveal the nature of a common denominator for the many apparently unrelated manifestations of cystic fibrosis in various organs of the body.

Collaborative experiments by Institute scientists and grantees at Columbia University have isolated an unknown gummy substance from the duodenum of patients with the disease. The substance is an abnormal mucopolysaccharide and is presumed to lend the special viscous nature to the pathologic mucus secretions in cystic fibrosis; its chemical characteristics are presently under investigation. The scientists have also found abnormal, viscous glycoprotein compounds in the urine of cystic patients and have partially determined the chemical characteristics of these compounds.

The biosynthesis of abnormal polysaccharides is being investigated by Institute scientists with the aid of a natural model for mucus formation, the hen oviduct. So far, a series of hitherto unknown sugar compounds, suspected of being precursors of active polysaccharide components, has been isolated. With the use of this newly unfolding biosynthetic system it is hoped that it will be possible to define biochemically the step-by-step mechanism of mucus formation.

Along with such basic investigations, which lay the foundation for future practical advances, work along clinical lines has produced much progress in the day-to-day therapeutic management of cystic fibrosis patients. During the past year approximately 100 patients have been studied and treated by the Institute's Pediatric Metabolism Branch. Of this number, 62 were hospitalized while the remainder were admitted as outpatients.

Measles represents a severe and at times fatal complication of cystic fibrosis. In an effort to give patients all possible therapeutic support, Institute clinicians in collaboration with the Division of Biologics Standards immunized 30 cystic fibrosis children with the new live measles vaccine, early in its development. Studies performed before and after the vaccinations will help determine the degree of protection offered by the new vaccine against otherwise serious complications.

In another clinical advance during the past year, an Institute grantee has improved a new method of inhalation therapy which involves the use of liquid aerosols containing 3 percent sodium chloride. Preliminary trials of this treatment, administered during the patient's sleep, have demonstrated that it can increase drainage of thick mucus secretions from the lungs. The same investigator is also evaluating the use of a newly developed vibrator device which shows promise in promoting lung drainage.

One of the manifestations of cystic fibrosis is the impairment of the intestine's digestive function. In order to clarify and evaluate this defect, a relatively simple but accurate test to measure the degree of intestinal fat absorption has been devised and perfected. This test employs the use of a readily available, inexpensive iodinated fat; a simple clinical test of urinary iodine determines precisely the extent of the patient's ability to digest and absorb fats.

These and other developments in diagnosis and therapy are being quickly transmitted to practicing physicians and research workers throughout the country. One particularly effective means of communication has been a specially prepared, comprehensive scientific exhibit on cystic fibrosis. This exhibit, along with detailed, practical literature concerning the most recent and effective forms of diagnosis and therapy, has been brought to attention of thousands of physicians at medical meetings throughout the country.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

A complicating factor of cystic fibrosis is pulmonary infection which, past surveys have indicated, causes approximately 90 percent of the deaths of cystic fibrosis patients. The most common pathogen involved in these recurrent infections is the Staphylococcus.

Clinical trials at the National Institute of Allergy and Infectious Diseases during the year should prove a significant contribution to the improvement of management of this aspect of the disease. Institute scientists continued to obtain good clinical results from the administration of dimethoxyphenyl penicillin. They also initiated clinical trials of another experimental penicillin resistant to the enzyme, penicillinase, which constitutes the major factor in the mechanism of drug-resistance. In addition to offering the distinct advantage of oral administration, this as-yet-unnamed antibiotic from Bristol Laboratories appeared 5 to 10 times more effective than dimethoxyphenyl when tested in vitro in the laboratory. Treating 15 difficult cases of staphylococcal infection, our clinicians have obtained cures or marked improvement and have observed only minimal side effects.

There are other complicating factors: in spite of many etiological, clinical and pathological differences between asthma and cystic fibrosis, there are many similarities in the pulmonary manifestations of both conditions, which may coexist in the patient. Similarly, the upper respiratory tract mucosa may respond to both cystic fibrosis and allergy. In a patient with chronic respiratory manifestations, the diagnosis of cystic fibrosis may be overlooked and the clinical impression of allergy may be misleading, until the basic diagnostic procedures, such as sweat-electrolyte analysis and allergy skin tests support the history and clinical findings. On the other hand, the patient with cystic fibrosis may develop allergic manifestations, which should be investigated and treated concurrently. One of the studies supported by the National Institute of Allergy and Infectious Diseases has underlined these aspects of the disease and, in an issue of the Journal of the

American Medical Association, alerted physicians to the importance of considering cystic fibrosis in the diagnosis of patients with recurrent respiratory tract disease symptoms. Investigations by the grantees at Harvard Medical School established that a large percentage of cystic fibrosis patients had originally been diagnosed as respiratory allergy cases. They also demonstrated the possibility of masked, and therefore, untreated respiratory allergy.

The Children's Bureau of this Department's Social Security Administration with the cooperation of the National Center for Health Statistics, has published data on the extent of cystic fibrosis from a pilot survey in Massachusetts, New Hampshire and Vermont. A report on this survey was presented recently before the Maternal and Child Health Section of the 89th Annual Meeting of the American Public Health Association in Detroit.

In the area surveyed a total of 621 patients with cystic fibrosis received medical care at some time during the 8-year period of 1952 through 1959. The annual number of known cases increased about 57 percent. Also, the annual case load of the disease among children under 18 rose from about 12 per 100,000 population under 18 years of age in 1952 to 22 per 100,000 population in 1958. During a 7-year period the number of patients with cystic fibrosis doubled for the age group under 5, tripled for the age group 5–9 years, and quadrupled for the group 10 years and older.

The figures are encouraging in as much as they show that early diagnosis and improved treatment is allowing children with cystic fibrosis to live far longer than in the past. A preliminary rough estimate of the incidence of diagnosed cases in the pilot area is only 42 per 100,000 live births or 1 per 2,300 live births. This is a lower estimate than that given for the population in general. It excludes diagnosed cases in newborns who died before leaving the hospital, and represents data on patients under the medical supervision of either the pediatrician or clinic contacted by the survey.

This survey was financed by a research contract from the National Institute of Allergy and Infectious Diseases. Our Advisory Council is of the opinion that the survey provides a reliable index to the national magnitude of the problem on which to project future research efforts, and therefore should be limited to the three-State area.

TABLE OF OBLIGATIONS

National Institute of Arthritis and Metabolic Diseases

	Fiscal year 1959	1960	1961	1962, estimated	1963, estimated
Extramural	$404,000	$485,159	$478,000	$800,000	$1,000,000
Intramural	25,000	50,000	85,000	100,000	100,000

National Institute of Allergy and Infectious Diseases

	Fiscal year 1959	1960	1961	1962	1963, estimated
Extramural	$382,500	$336,800	$240,100	$255,200	$300,000
Intramural	28,000	65,000	30,000	75,800	50,000

OSTEOPOROSIS

Mr. FOGARTY. What is osteoporosis?

Dr. DAFT. That is when calcium is lost from the bones, and the bones become more brittle and more likely to fracture, particularly in old age.

Also when you treat patients with rheumatoid arthritis with the corticosteroids, some of these steroids unfortunately have as one of the side effects the loss of calcium. One of the very serious complications in the treatment with steroids is the breaking of the vertebrae of the back, a collapse of the vertebrae because of the thinning, the osteoporosis of the bones.

Mr. **Fogarty**. What is the most serious form of arthritis or rheumatism?

Dr. **Daft**. I might answer that in two ways, sir. The most serious in regard to a fatal outcome are fortunately some of the rarer of the diseases. There are a number of those which are likely to lead to death in the near future without steroids.

Mr. **Fogarty**. Death is not generally connected with rheumatism or arthritis, is it?

Dr. **Daft**. Not with rheumatoid arthritis. Here I think in a way we would consider rheumatoid arthritis the most serious of the diseases for two reasons, one being the number of people afflicted by it and, second, the seriousness of the disease even though it is not a killer.

OSTEOARTHRITIS

Mr. **Fogarty**. What about osteoarthritis?

Dr. **Daft**. Osteoarthritis is another serious disease.

Mr. **Fogarty**. You know more about rheumatoid arthritis than you do about osteoarthritis, do you not, or you can do more; is that right?

Dr. **Daft**. We can do more, yes, sir. Osteoarthritis is being studied all the time along with rheumatoid arthritis. It also exists in a very large segment of the population. It has been stated that every individual who lives long enough gets some osteoarthritis. That is a little damage to the joints, the tissues around the joints.

Mr. **Fogarty**. It gets to be pretty serious, does it not?

Dr. **Daft**. In some cases it is extremely serious and extremely painful. Fortunately, in a large majority of the cases it is not as severe as that, but there can be a great deal of bone destruction in osteoarthritis, and it becomes very painful and also very crippling.

1963 BUDGET PROPOSALS

Mr. **Fogarty**. Your appropriation for 1962 is $81,831,000. The request for 1963 is $91,921,000.

Dr. **Daft**. Yes, sir.

Mr. **Fogarty**. What did you do to deserve such extraordinary treatment? Is this a real increase of over $10 million?

Dr. **Daft**. Yes, sir; there is a very good increase here particularly in the area of research grants.

Mr. **Fogarty**. You are still about $12 million short of what you asked for, however?

Dr. **Daft**. Yes, sir.

RESERVE OF 1962 APPROPRIATIONS

Mr. **Fogarty**. The reserve from this year's appropriation is $5,085,000. How much of that is forced savings?

Mr. **Seggel**. $4,508,000.

EFFECT ON RESEARCH PROGRAM

Mr. **Fogarty**. They really forced you to save a lot of money this year. Do you have more research grant money than you need to finance the approved applications?

Dr. Daft. No, sir; we do not.

Mr. Fogarty. I have a table here that shows, for 1962, you are $1,871,000 short of being able to finance all approved applications; right?

Mr. Seggel. The projected total requirement in 1962 amounts to $4,718,000, but we only have a reserve of $3,716,000 in research grants. That is the total reserves. So that even if we released the total reserves, we could not finance that total of $4.7 million.

Mr. Fogarty. I see now. I was looking on the wrong line. The shortage I gave would be the shortage even if your reserve was released. You are being treated worse than any other institute, are you not, in 1962? That is what the record shows anyway. I thought this was an area where we had a long way to go to catch up. Instead of that, they are cutting you back. It does not make sense to me.

EFFECT ON TRAINING PROGRAM

Do you have requests for good training programs that you cannot finance?

Dr. Daft. Yes, sir.

Mr. Fogarty. Will you supply for the record some examples?

Dr. Daft. Yes, sir.

(The information follows:)

The National Institute of Arthritis and Metabolic Diseases has traditionally supported training programs in arthritis, diabetes, endocrinology and metabolic diseases, hematology, nutrition, and gastroenterology. In recent years support of graduate training in dermatology, pediatrics, and orthopedics has been added to the list. We estimate that on the basis of current training grant committee and Council recommendations we have approximately $500,000 worth of approved graduate training grant applications, 15 to 20 in number, for which there will be no funds during the current fiscal year. As the result of this insufficiency, the Institute will find itself unable to start several deserving and much needed training programs in pediatrics, one outstanding program in orthopedics, and several meritorious hematology programs, applications for all of which have been received during the current year.

Similarly, last year the Institute was unable to pay out approved fellowship applications for over 100 well-qualified young scientists interested in research careers—while currently over 200 approved fellowship applications cannot be financed because of the lack of funds.

SHORTAGE OF TRAINED PERSONNEL

Mr. Fogarty. Is there still a shortage of trained people in this field?

Dr. Daft. Very definitely, sir.

Mr. Fogarty. Will you supply for the record a statement on need for trained people and how much money you think we ought to appropriate over the budget in 1963 to get a good program going in this area?

Dr. Daft. I should be very happy to.

(The information follows:)

In order to meet a very conservative estimate for manpower in the various areas of this Institute's categorical responsibilities, on a long-range basis, it would be necessary for us to provide approximately 1,200 trainee positions next year under our training grant program. Our current program provides for approximately 850 trainees. An increase of $1,475,000 in training grant money and $2,323,000 for fellowships represents an extremely conservative estimate of additional funds needed to achieve the desired goal.

To attest to the fact that candidates would be available for such training positions, approximately 60 percent of program directors in a recent survey in diabetes, endocrinology and metabolic diseases, arthritis, gastroenterology, and dermatology, indicated that, were funds available, they could have appointed more trainees of good quality under their training grants. The survey is incomplete as yet and does not include nutrition, hematology, pediatrics, or orthopedics programs directors, but those reporting indicated some 375 potential trainees could have been added to their programs had funds been available for their stipends. Of the programs directors who have reported to date, it should be acknowledged that these individuals are in the best position to evaluate the existing situation, approximately 75 percent indicated their present professional staffing patterns (experienced staff personnel to provide the actual training) were inadequate to accomplish the goals of their academic responsibilities; 90 percent of these same program directors pinpointed shortages specifically in the research personnel category.

Mr. Fogarty. Is there unused potential for training that could be used if funds were available?

Dr. Daft. Yes, sir.

Mr. Fogarty. No question about it?

Dr. Daft. No, sir; no question.

MOLECULAR BIOLOGY

Mr. Fogarty. The committee said in last year's report we thought the whole field of molecular biology needs strong support. Did you agree with that statement?

Dr. Daft. Yes, sir.

Mr. Fogarty. What are you doing about it?

Dr. Daft. We are starting a new laboratory in this area in Bethesda, as well as supporting this very heavily throughout the United States.

Mr. Fogarty. Tell me a little bit about it.

Dr. Daft. One of the important areas in the field of molecular biology is in genetics. This was the field on which I touched in relation to breaking the genetic code.

Mr. Fogarty. What about the lab?

Dr. Daft. When we inherited a little more space from the Dental Institute when they got their new building in Bethesda——

Mr. Fogarty. You are not going to crowd them out of their new building, are you?

Dr. Daft. Not in the new building. They did not need the space in their old building. We inherited a little bit of space in the old building. This is one of the areas we are putting a great deal of emphasis on in our new space in the old building, the field of molecular biology. The man who broke the genetic code first at Bethesda is attached to this laboratory. I might say this is a field which has had a great deal of interest in the press. I do not know whether you happened to notice the front page article in the New York Times and a full page a little later, covering the earlier findings in this area plus our new findings.

Mr. Fogarty. Dr. Shannon mentioned this. We put it in the record, I believe. So you are making real headway?

Dr. Daft. Yes, sir.

SKIN DISEASE RESEARCH

Mr. Fogarty. We also pointed out the whole field of skin diseases is relatively neglected and indicated we thought more should be done.

Dr. Daft. We are doing a great deal more, sir, both in the area of research and research training. We had a meeting very recently of the program directors in this field who went over progress that had been made in the last year and needs for the future. I think that the fundamental understanding of skin diseases—by that I mean not on the clinical level, but on the basic level—needs a very great deal of research done.

Mr. Fogarty. Is there any overlapping between you and Dr. Andrews in this area?

Dr. Daft. I believe none whatever in this area.

Mr. Fogarty. You have not made much progress, have you, since you appeared before us?

Dr. Daft. It is a beginning program, and there are no specific things that I can point to as being of tremendous progress in this area; no, sir. We have built the program up, and most of these people are evolving teams which consist of a clinician—which is, of course, the first requisite—but also basic scientists in the team, who will, hopefully, over the next year and several years, give us a better understanding of skin diseases.

Mr. Fogarty. You can expand on that statement about what you are doing in this field.

(The information follows:)

Dermatology

In the study of diseases related to the skin, this Institute's programs have been continuously increasing since we first took responsibility for this area. As the number of institutions and investigators qualified to conduct the research in this area increases, it becomes ever more apparent that before real headway in specific skin disease control is to be practical, much basic understanding of the skin as a biological tissue is necessary.

Toward this end we presently support many studies concerned with metabolism within the skin and how this is influenced by the use of drugs whether applied locally, by mouth or by injection. Also, numerous morphological studies of skin are underway both in the normal human and in diseased human skin as well as in experimental animals by way of comparison with the human. It is a little appreciated fact that there are striking similarities between certain processes occurring in man's skin that are common to other forms of life.

Beyond the basic areas are those far closer to immediate clinical application. We are supporting studies relating to burns, including those of the X-ray type induced in treatment, or by the ultraviolet rays in sunlight as in sunburn. Recently the problems of the contact dermatitis-producing agents, which are such a concern to industry, have received additional research attention and support. The disfiguring and aggravating diseases such as acne, boils, psoriasis, and erysipelas are also receiving attention both better to understand the problems and to alleviate their effects.

Like the formed elements of the blood, the skin has been recognized as a relatively easily accessible human organ exhibiting many complex structures and metabolic functions. Fortunately for dermatology and for other branches of medicine which rely upon dermatology to interpret the manifestations of systemic disease in the cutaneous system, this awakening of interest in research in dermatology is attracting some of the best of the recent medical school graduates. With advanced training in a stimulating atmosphere of dermatology training grant centers, these academicians of the future will identify a more basic and broader body of knowledge as dermatology and serve not only their own field well but all of medicine. With the experience of developing other programs for research training in clinical departments in the medical schools, the dermatology training grant program has been patterned somewhat along the lines that other programs, such as hematology and gastroenterology have developed. Problems in attracting well-qualified young physicians as trainees, relationships with basic science departments, the characteristics of a suitable training grant program director, have been tackled with a leading group of academic dermatologists. The definition of the role of dermatology in relation to the medical community as a whole has been focused upon in the context of the training grant program.

1963 BUDGET FOR RESEARCH GRANTS AND TRAINING

Mr. Fogarty. Ninety-five percent of your increase for 1963 is for research grants, but I see it is less than half the increase that would be required to finance all new approved applications; is that right?

Dr. Daft. That is correct.

Mr. Fogarty. You do not have any increase in here for training?

Dr. Daft. No increase for training.

Mr. Fogarty. No increase for fellowships?

Dr. Daft. No, sir.

Mr. Fogarty. This runs all the way through the National Institutes of Health. Mental Health came out with a small increase for training but everybody else—this looks like outright discrimination to me.

ORAL THERAPY FOR DIABETICS

What about your progress in oral therapy for diabetes?

Dr. Daft. That has continued, and I am very happy to report that some of the findings of the past year, which were beginning a year ago when I spoke to you, these have been developed further and as a result a greater proportion of patients are benefiting from the oral therapy. The progress has been largely in the area of a combination of drugs.

There are two types of oral drugs that are used against diabetes. One is a sulfonamidelike drug and the other is of entirely different structure. When they are used alone, they are effective in only a certain number of cases of diabetes. It has been found they can be used in combination and that many patients who will respond only for a time to one of the drugs will respond to both of the drugs much more successfully.

Our best figures indicate that now about 2 out of 5 patients with diabetes benefit and can be controlled successfully on the oral drugs. This is a good increase—last year we said about a third of the patients—but the difference between 33⅓ and 40 percent is very large in number of patients. Now about 40 percent of the patients are benefiting from the oral drugs.

We are continuing a long-range study. All I can report on the long-range study is that it is progressing satisfactorily, but we want to know exactly how good the oral drugs are in preventing the complications of diabetes which develop after many years. It is very hard to be certain that the oral drugs are as effective as insulin in preventing these late-occurring complications. So this of necessity has to be a long study. But this study, which involves some eight of the medical schools, is progressing very well, and we will have for you, sir, an answer after some years, however.

Mr. Fogarty. How long have we been using insulin?

Dr. Daft. I think insulin started about 1920.

Mr. Fogarty. Who discovered it?

Dr. Daft. Banting and Best and McLeod in Canada.

Mr. Fogarty. It has saved a lot of lives, has it not?

Dr. Daft. Yes, it certainly saved a tremendous number of lives.

GASTROENTEROLOGY

Mr. Fogarty. What are you doing in the field of gastroenterology now?

Dr. Daft. We are continuing both the program of research and research training in gastroenterology.

Mr. Fogarty. Dr. Barborka does not think you are doing enough.

Dr. Daft. I have discussed this matter with Dr. Barborka. I am quite certain you will find that he feels that the progress we are making and the difference between the support of this field now and a few years ago, when he appeared first before the committee and got you interested in this field, also helped to get us interested—it has been tremendous.

Mr. Fogarty. We put more money in the bill and told you to get to work on it, did we not?

Dr. Daft. Yes, sir; and we certainly have.

Mr. Fogarty. Was that a good investment?

Dr. Daft. It has been a very good investment.

Mr. Fogarty. Tell us about some of the things that have happened and some of the progress that has been made.

Dr. Daft. There has been progress in a great number of areas. I might pick out one in particular which is in the general area of gastroenterology and may seem at first glance trivial, but it is not. That is in the cases of damage to the liver due to biliary cirrhosis. The bile pigments do not escape into the gastrointestinal tract and are blocked up into the liver and escape from there into the general circulation and deposit in the skin. That leads to intractable itching.

As I say, this might appear trivial, but it is certainly not. The itching is so severe that it leads to suicide in cases. There has been a discovery in the past year of a very good method of preventing this. They use a material which sequesters the bile pigments, does not let them return to circulation, cuts down the amount in the bloodstream, and, therefore, in the skin, and have been able to solve this very distressing problem.

I might mention, in passing, that I once had jaundice from an infectious hepatitis, and to me the unbearable part of it was the itching. It is tremendous. So I can speak from personal knowledge as to the serious complication that this is in a case of hepatitis. That has been one of the things that has happened.

They are in the process of developing new instruments which are able to tell the site of lesions, such as a peptic ulcer. The instruments are swallowed and the lesion is visualized. It is hoped this method will allow doctors to locate the defect and intervene, when it is necessary, with surgery.

There has been a new method worked out to treat obstructions which hitherto have been treated only by surgery, which is quite drastic. Our grantees have found a method, the details of which I cannot reproduce for you, but which I can supply, which permits them to cure obstructions without surgery.

Mr. FOGARTY. Does the whole problem of ulcers come in this category?

Dr. DAFT. Yes, sir.

Mr. FOGARTY. The incidence of ulcers seems to be on the increase. Is it because of the manner of living or what?

Dr. DAFT. Probably so. It is probably a very complicated thing and many things enter in.

Mr. FOGARTY. There was an article in the Daily News September 20, 1961, "Ulcers Now Labeled a Top Killer." It says the percentage change since 1950 is up 7 percent. That is a considerable increase; is it not?

Dr. DAFT. Yes, sir.

Mr. FOGARTY. What are we doing about it?

Dr. DAFT. This is one of the areas of gastroenterology where a great deal of work is going on and they are finding out more and more about the causes of ulcers. I should mention in passing our support in the field of gastroenterology which will give you some idea of how we have followed your advice. In 1961 the support was just under $7 million, which includes the total. If we go back to 1958, the support was $1,225,000. The support in 1961 increased from $1,255,000 to just under $7 million, and the estimate for the current fiscal year is nine and a quarter million. This gives you an idea of the amount of support which is being furnished. This includes research grants, fellowships, traineeships, training grants, and our intramural program.

Mr. FOGARTY. Maybe we ought to be spending $15 million.

What progress have we made in the study of ulcers?

Dr. DAFT. There is no specific progress, sir, in the past year to which I can point as being very great.

Mr. FOGARTY. What about surgical techniques? Are they improving?

Dr. DAFT. Surgical techniques are improving.

Mr. FOGARTY. If they do not respond, is that not the general thing to do?

Dr. DAFT. Yes, sir. The first thing, of course, is an attempt to manage the ulcer without surgery.

Mr. FOGARTY. Is that a serious operation? I suppose it all depends on the circumstances.

Dr. DAFT. If they have to make an anastomosis it becomes a serious operation, the effects of which may persist the rest of a person's life. Of course, if a malignancy is involved also, that is very serious.

Mr. FOGARTY. There is no way of telling whether it is malignant or not until an operation is performed?

Dr. DAFT. Frequently not, sir. Sometimes there are indications which give you an idea one way or another, but the only definite way of finding out may be when they go in. However, if they can manage the ulcer by diet, rest, et cetera, as they usually do, and see that the ulcer disappears, then they are quite certain there is no malignancy involved, so in this case one is quite reassured.

Mr. FOGARTY. Many times you clear up one and then you develop another one; is that not right?

Dr. DAFT. That is unfortunately true. As you say, it may have something to do with the life we lead today.

Mr. FOGARTY. Is there anything you can do that you are not doing now in this field?

Dr. DAFT. There are a number of areas where we are doing a great deal. As I mentioned, they have a number of new instruments to study what is going on in the gastrointestinal tract that might lead to ulcers, as well as study the activity. They have been studying the motility of the gastrointestinal tract and its secretory function and these have something to do with the production of ulcers.

They are learning a great deal more about that and how to control the hypersecretion and motility, partly by drugs and partly by other methods.

The gastric secretion has always been considered as having something to do with ulceration, and we are learning a great deal more about gastric secretion and how it is controlled by the body and what can be done about it.

They are also learning a great deal about hormonal control of the ulceration and a fourth one, of course, is drug therapy. There have been some drugs developed for the treatment of ulcers which have some promise. The only new drugs I have heard of in this area are derivatives of the first one, Banthine. Banthine was probably the trade name and some derivatives of Banthine have been developed. Those are the four principal areas in which research has been going on. A great deal of work is being done. As far as complete control of it, we certainly have not made progress.

PEDIATRICS

Mr. FOGARTY. What are you doing in the field of pediatrics?

Dr. DAFT. We are supporting some pediatrics training grants outside the Institute, usually for specific purposes, both in the training in our research area, research grants, and in our own research at Bethesda. One of our biggest areas of emphasis has been in the metabolic diseases of childhood.

Mr. FOGARTY. Will you expand on this and give us a complete story on what you are doing in the field of pediatrics?

Dr. DAFT. Yes, sir.

(The requested information follows:)

RESEARCH AND TRAINING IN PEDIATRICS

The National Institute of Arthritis and Metabolic Diseases pursues a very active program of research in pediatric diseases in its laboratores and clinics in Bethesda. This includes studies in cystic fibrosis, galactosemia, celiac disease, and related malabsorption disorders in children, cystinosis and other inherited metabolic diseases in children, childhood endocrine diseases, juvenile anemias, juvenile rheumatoid arthritis, and juvenile diabetes. Concurrent with this clinical work, very extensive basic research is aimed at the fundamental mechanisms involved in these and other childhood diseases.

Extrmurally, research support is extended to numerous investigations in cystic fibrosis, special anemias of infancy, acidosis of the newborn, physiology of pediatric surgery, fluid and electrolyte balance in infantile diarrheas, juvenile nephritis and rheumatoid arthritis, juvenile hypoglycemia, physiology of premature infants, infant nutrition, juvenile diabetes, and endocrine disorders of childhood.

In the area of research training, the Institute supports 18 active training grant programs in departments of pediatrics at various medical schools. In addition many NIAMD training programs in other departments (such as in medicine and its subspecialties) impinge strongly on the pediatric field since a large number of metabolic, endocrine, hematologic, and familial diseases manifest their most severe symtomatology in the very young.

HEMOPHILIA

Mr. FOGARTY. In the area of hemophilia, what are you doing? Are you doing research on it?

Dr. DAFT. Yes, sir. There is a development in the field of hemophilia which has not resulted yet in any scientific publications, but I had a report from one of the investigators at Bethesda very recently which points up a very striking advance in this field. I am not certain it is published. Might I discuss this off the record and then we will decide whether to put it on the record?

Mr. FOGARTY. Yes.

(Discussion off the record.)

GERM-FREE RESEARCH

Mr. FOGARTY. Will you supply for the record a statement on what you are doing in germ-free research?

(The information requested follows:)

GERM-FREE RESEARCH

Research involving germ-free animals in the laboratories of the National Institute of Arthritis and Metabolic Diseases involves primarily problems associated with nutrition, nutritional requirements, and the role played by the natural intestinal microbial population in supplying essential nutrients to the animal host—and by inference—to man. These studies have demonstrated to date that significant quantities of essential vitamins, folic acid, thiamine, pantothenic acid, and other vitamins of the B complex group are synthesized by the intestinal microflora and are absorbed from the intestine and utilized by the host animal. In germ-free animals, specific nutritional deficiency symptoms (including liver cirrhosis and necrosis) can be precipitated by appropriate diets since these animals are not the recipients of the nutritional contributions of a natural intestinal microflora. A number of these studies are being conducted in collaboration with scientists at Walter Reed Army Medical Center.

Another investigation involving germ-free animals concerns rheumatoid arthritis. Preliminary results have shown that it is possible to induce joint lesions in the experimental animal which resemble those of rheumatoid arthritis in all respects, by the injection of Freund's adjuvant—a sterile preparation of products of the tubercle bacillus, dispensed in a lipid medium, which is known to enhance immune reactions nonspecifically when injected in mammals. Such experiments have previously resulted in rheumatoid arthritislike joint lesions in regular experimental animals; their elaboration in the germ-free animal significantly emphasizes the fact that infection or presence of micro-organims in the host animal is not essential to the elaboration of rheumatoidlike joint lesions.

The National Institute of Arthritis and Metabolic Diseases presently supports studies involving germ-free animals at four universities, in addition to long-term support of the development of germ-free animal colonies and techniques at Notre Dame University. Among the subjects under investigation are the role of the intestinal microflora in the aging processes of the host, the effect of the pituitary antidiuretic hormone (pitressin) on intestinal permeability, the formation of gamma globulin in germ-free hosts, and the pharmacologic and possibly therapeutic effects of naturally occurring amines on peptic ulcer, regional enteritis, ulcerative colitis, sprue, the irritable colon syndrome and hepatic coma.

OSTEOPOROSIS STUDY

Mr. FOGARTY. What is osteoporosis? You mentioned it earlier, but tell us a little more about it.

Dr. DAFT. Yes, sir. That is a loss of calcium from bones which makes them brittle and more likely to fracture. It occurs in very many older people; if they are not on the right diet or perhaps for other reasons, they may lose calcium from their bones. It make them much more liable to breaking and it is very serious, of course.

Mr. FOGARTY. Are you making any headway on it?

Dr. DAFT. Yes, sir. One of our investigators at Bethesda has been studying this for some time, both as it occurs in older people and also as a side-effect of corticosteroid therapy, usually for rheumatoid arthritis.

Mr. FOGARTY. Is it very prevalent?

Dr. DAFT. It is quite prevalent in older people. The degree of it is what varies a great deal. The very serious cases are not extremely prevalent, but there is often some degree of calcium loss from the bone, and this goes back a little bit to what you were talking about with the Dental Institute. That is one of the very fine things about milk; it has a large amount of calcium in it. Milk, of course, is a very good food in many ways. It contains very good proteins, vitamins, and a large amount of calcium.

STUDIES IN NUTRITION

Mr. FOGARTY. Are you doing very much work in the field of nutrition?

Dr. DAFT. Yes, sir, both in the laboratory at Bethesda and elsewhere.

Mr. FOGARTY. Give me a short summary and you can expand on it for the record.

Dr. DAFT. The Interdepartmental Committee for Nutrition was mentioned in the testimony by the Dental Institute and we have prepared a special report on that, which we thought would be of considerable interest to you. The international nutrition activities have been proceeding extremely well. Many surveys have been carried out. We have made recommendations as to what should be done, and have gone back in some cases a few years later and found out that there has been a remarkable change.

Mr. FOGARTY. Will this ruin the vitamin business?

Dr. DAFT. No, sir.

Mr. FOGARTY. If it is a good report, it ought to, I would think. I thought you people always preached that if everyone ate the right things there would not be need for vitamin pills.

Dr. DAFT. That is correct, sir. If everyone had the right diet, there would be no need for vitamin pills. On the other hand, we have all been in favor of the fortification of bread and flour with vitamins because even the American diet may not have all that it should have of certain of the vitamins. Therefore, vitamins and iron are being added to most of the bread and flour in this country.

Mr. FOGARTY. What about the millions of people who are on diets and have given up bread?

Dr. Daft. In the case of people on restricted diets, I should modify my previous remark; they probably do not get enough vitamins. Lots of people on special diets, particularly on dietary fat restriction, may not get enough vitamins.

Mr. Fogarty. You can expand on that.

(The requested additional detail follows:)

Special Report: International Nutrition Activities

Introduction.—The basic purpose of the international nutrition activities of the National Institute of Arthritis and Metabolic Diseases (NIAMD) is to accumulate fundamental scientific data directly related to our understanding of diseases of importance to the public health of the United States and to our medical and allied science research and teaching at home and abroad and to participate through support of selected research projects, through direct and collaborative laboratory and field studies, and through joint action with the Interdepartmental Committee on Nutrition for National Defense (ICNND) and other institutions and agencies, in the evaluation and improvement in the nutritional health and well-being of the peoples of developing nations. To these ends, maximum emphasis is placed upon extensive collaboration with the scientific communities and local governments in conducting nutrition studies and in preparing and implementing recommendations utilizing the resources of the countries in question. These purposes are attained by approaching nutrition from all angles: those of medicine and dentistry, biochemistry, dietetics, food technology, and agriculture. These same approaches are used for all population groups be they civilians—infants, schoolchildren, pregnant women, the elderly, and the sick—or members of the armed forces devoted to the internal security and defense of their countries.

The international responsibilities of the National Institute of Arthritis and Metabolic Diseases in nutrition research were incorporated into the Institute at its formation. Dr. W. Henry Sebrell, Jr., the Institute's first Director and subsequent Director of NIH, has long been one of the world leaders in nutrition research before he assumed leadership of this Institute. When the Institute was founded, one of the Public Health Service's oldest and most venerable laboratories, the Laboratory of Biochemistry and Nutrition, was one of the four units that formed its nucleus. Dr. Floyd S. Daft, the present Institute Director, was Chief of the Laboratory at that time. Dr. Daft, too, had extensive international interests in nutrition and received an important part of his training at the Carlsberg Laboratory of Copenhagen, Denmark. As Director, Dr. Daft maintained his own associations abroad and encouraged nutrition scientists of the Institute to form important associations and collaborations with other nutritionists throughout the world. An example of this is the first International Symposium on Nutritional Factors and Liver Diseases, held in New York City in 1953. This symposium, the first of its kind in this important area, was initiated and chaired by an Institute scientist. However, it was not until 1955 that the Institute entered broader programs of actual support of nutrition research abroad.

In that year the Institute began to support studies of protein malnutrition in Central America. In that year, too, on the initiative of the late Dr. Harold R. Sandstead, the ICNND was formed to provide coordination at the Federal level of technical aid programs involving nutrition in developing nations. The NIAMD became a principal partner in ICNND and in addition provides offices and administrative services for this Committee.

The international activities of the NIAMD encompass the award of research grants abroad, collaborative projects with foreign universities and research institutions, field studies manned by staff members of NIAMD, and participation in the activties of ICNND. In addition there are active Public Law 480 fund supported projects in the fields of international nutrition and public health, on which a number of Institute scientists serve as project officers. A detailed accounting of these international nutrition activties of NIAMD follows, except for Public Law 480 activities which are covered in a separate report.

Interdepartmental Committee on Nutrition for National Defense

Organization.—The ICNND, established in 1955, is formed by representatives from the Departments of State; Health, Education, and Welfare; Defense; Agriculture; the Agency for International Development; and the Atomic Energy

Commission. Dr. Frank B. Berry, Deputy Assistant Secretary for Defense, Manpower (Health and Medical), has been Chairman of the Committee since its organization; Dr. Floyd S. Daft, Director of NIAMD, is Vice Chairman of the Committee. Dr. Arnold E. Schaefer (NIAMD) is the Executive Director, and he and his staff form the Secretariat of the Committee. The Secretariat operates administratively through the NIAMD and is located on the campus of the National Institutes of Health. The Committee is advised and guided by a large group of special consultants from universities and private and Federal agencies throughout the United States, covering the fields of clinical medicine and dentistry, nutritional biochemistry, dietetics, agriculture, and food technology.

Purpose.—The primary objective of the ICNND is to assist developing countries to assess their nutritional status, to define their major problems in this field, and to develop recommendations for the maximum utilization of the countries' resources to meet their critical nutritional problems.

A secondary outgrowth of ICNND surveys is the training of local counterpart personnel in the scientific aspects of the Committee's work, and assistance to countries by furnishing the necessary laboratory equipment and supplies for use in continuing nutrition studies.

Methods of operation.—Following an official request from the country concerned, transmitted through State Department channels, the ICNND and the Government of the host country organize a team of nutrition scientists from the laboratories and universities of both countries (usually about 15 Americans and 2 to 3 times this number from the host country). This team then undertakes an extensive survey of each aspect of nutrition throughout the country, from which results a detailed scientific report both in English and the national language, with recommendations centering about self-help programs designed to improve the nutritional status of the local population. Every effort is made to coordinate recommendations with existing and envisioned programs of the host country and the United States, and to work in close collaboration with the United Nations, agencies and other groups concerned with health and nutrition (particularly WHO, FAO, and UNICEF). Other important aspects of the assistance program of the ICNND include the invaluable scientific training of counterpart colleagues in nutrition evaluation techniques, the establishment of a permanent medical nutrition and food laboratory in the country with all initially required equipment and supplies provided by the ICNND, and provision of consultative services at their request through the months and years subsequent to the survey to further stimulate, amend, and augment recommendations and to cope with specific technical problems as they arise. In collaboration with the countries where the ICNND has worked, the ICNND cosponsors international nutrition conferences to stimulate the exchange of fundamental scientific ideas and information pertaining to the current status of nutrition programs and research in these various countries.

A total of approximately 300 specialists furnished by 32 American universities, colleges, research, and other institutions, and 24 U.S. governmental agencies have taken part in the Committee's activities. In addition, seven other nations have provided team personnel to work in countries other than their own. These include Turkey, Spain, the United Kingdom, Colombia, Canada, Ireland, and the Netherlands.

Since its organization 7 years ago, the ICNND has conducted nationwide nutrition surveys in 18 foreign countries: the Republic of Korea, the Republic of China, the Philippines, the Republic of Vietnam, Thailand, Burma, Pakistan, Iran, Lebanon, Turkey, Ethiopia, Libya, Spain, Peru, Ecuador, Chile, the West Indies, as well as Alaska before statehood. These surveys and related activities have resulted in gradual development of special literature containing a vast fund of scientific nutrition information of widespread international scope, available at no cost to nutrition groups, Government agencies, and similar institutions throughout the free world.

ICNND activities during fiscal year 1962.—The oversea activities of the ICNND during the first 6 months of fiscal year 1962 are outlined below:

(1) Nutrition survey of the Federation of the West Indies (August–September 1961).

(2) Nutrition survey of the Union of Burma (October 1–December 15, 1961): The vast amount of scientific data obtained in these surveys are being processed, assembled, and interpreted, and recommendations are being prepared by the teams for presentation to the appropriate authorities. These reports will be completed and presented before the end of fiscal year 1962.

(3) The results of the 1960 resurvey of the armed forces of the Republic of China were presented and reviewed in Taiwan in July 1961 by Lt. Col. Irvin Plough (USA–MC), the team director. The results of this resurvey—4 years after an initial survey and recommendations—gave forceful testimony to the value of the ICNND programs. The resurvey revealed dramatic improvement in the nutritional status and general health of the armed forces, resulting from the actions taken by the Republic to implement recommended programs for improvement. The key to this improvement was the construction of two rice enrichment plants and the introduction of such rice into the military ration.

(4) The results of the 1960 survey of the civilian population and the armed forces of the Kingdom of Thailand were presented and reviewed in Thailand in November 1961 by Dr. Allan L. Forbes (NIAMD), the team director. Emphasis was laid upon the need for introduction of a national salt-iodization program to bring goiter due to iodine deficiency under control. The team brought to light a number of areas warranting further clinical and food research. Scientist-to-scientist negotiations are now underway to extend activities into studies on the high infant mortality, vitamin B_1 and B_2 defiency, bladder stones in children, anemia, dental nutritional disease, and goiter—problems of fundamental importance to the people of Thailand as well as to the entire world medical community.

(5) A text of food composition tables for use in Latin America, giving individual nutrient contents for over 700 foods common to that area was published in October 1961. The English, Spanish, and scientific names for all food items are given; no such comprehensive text for South and Central America existed prior to its publication.

(6) Our understanding of the nutritional relationships to infectious disease is very meager indeed. The same applies to many aspects of the availability and absorption of essential nutrients—for example, iron—in the gastrointestinal tract. As a consequence, ICNND–NIAMD have joined forces in Cairo, Egypt, with Vanderbilt University and the U.S. Naval Medical Research Unit No. 3 (NAMRU 3) to study the relationships of nutrition to the anemias observed in a number of infectious and parasitic diseases over the period of the next 4 to 5 years. Egyptian and American scientists are working together on these projects, and Dr. Harold H. Sandstead, an ICNND–NIAMD medical officer and son of the first Executive Director of ICNND, the late Dr. Harold R. Sandstead, is now in full-time residence in Cairo. This project will be continued under a Public Law 480 agreement with NAMRU No. 3 and the Government of Egypt.

(7) Followup visits by the ICNND consultants and Institute personnel have been made to many of the countries previously surveyed, as well as to the countries scheduled for the remainder of fiscal year 1962 and to countries that have expressed the desire to undertake collaborative work with the ICNND. The results of such visits are too numerous to discuss individually, but a few examples are:

(*a*) Firsthand evaluations of the rice shortage problem in Vietnam and particularly the acute shortage in the city of Saigon were provided to the State Department and other concerned agencies in December. Other ICNND activities are currently underway in Vietnam in consultation with the Department of Defense.

(*b*) Technical assistance in the fields of nutritional biochemistry, dietetics, and dietary survey techniques were provided to the National Institute of Nutrition in Quito, Ecuador, by consultant visits during the fall of 1962 in collaboration with WHO.

(*c*) Continuing assistance to the armed forces of Korea and to U.S. military assistance groups in Korea was provided by consultant visits in November 1961. The nutritional status of the Korean forces has improved tremendously as the result of implementation of the recommendations to the two surveys of 1953 and 1956.

Some of the major ICNND activities scheduled for the remainder of fiscal year 1962 are listed below:

(1) Nutrition survey of Uruguay (February 20 to May 5, 1962).
(2) Nutrition survey of Jordan (April 1 to June 15, 1962).
(3) Nutrition survey of Bolivia (May 15 to August 15, 1962).

The teams for the first two above are now fully organized, and their briefing session was held jointly January 11–13, 1963. Final aspects of organization of the Bolivia team is now in progress in Bolivia and the United States.

(4) The ICNND and the Government of the Republic of Vietnam are jointly organizing and sponsoring the Far East nutrition symposium which will take place in Saigon March 11–17, 1962. Fourteen nations from the rice economy portions of the world will be represented as well as the United States and three United Nations agencies (WHO, FAO, and UNICEF).

(5) The ICNND and the Government of Spain are jointly organizing and sponsoring the Fifth Armed Forces Internation Nutrition Conference to be held in Madrid April 24–30, 1962. Twelve nations from the Middle East, the Mediterranean, and South and Central America will be represented as well as the United States and the United Kingdom. The ICNND in conjunction with the countries concerned has previously sponsored four such conferences, held in Teheran, Iran (1956) : Ankara, Turkey (1958) ; Rawalpindi, Pakistan (1959) ; and Denver, Colo. (1960).

(6) The results and recommendations of the surveys on Burma and the West Indies Federation will be presented to the appropriate authorities.

(7) Consultative services in the fields of dietetics and dietary survey techniques will be provided to Turkey during the spring of 1962. Similar services are being extended to Pakistan this winter and spring.

Looking ahead to fiscal year 1963, the ICNND has received expressions of interest for collaborative nutrition evaluation and research studies from Brazil, Malaya, Nigeria, Korea (to extend work into the civilian population), Venezuela, and Ghana. Requests for consultation, and general and technical assistance, have been made by numerous other countries previously surveyed.

Some examples of ICNND recommendations and undertakings (prior to fiscal year 1962 are not discussed above) which have been implemented into particularly effective programs are listed below for background purposes:

1. Development of a comprehensive multilanguage handbook (Manual for Nutrition Surveys) for survey team use in collecting data for and evaluation of nutritional status of population groups.
2. Quality control and specifications for food processing (taken for granted by food purchasers in the United States) have been introduced in five countries where they had not existed before.
3. Three canning plants have been opened in Iran with two more scheduled to begin operation. Four milk-processing plants have also been opened.
4. Field rations for troops have been developed where they did not previously exist and a new armed forces nutrition laboratory was recently dedicated in Iran.
5. Development of special clinical teaching slides depicting major nutritional deficiency lesions.
6. A modern packing plant has been opened, and controlled enrichment of fats and oils with vitamin A has begun in Turkey. Pilot studies have been initiated in Turkey toward enrichment of wheat flour.
7. Continuous medical and biochemical appraisal of the ration system in armed forces is now well established in Korea.
8. Nutrition courses have been established in the College of Agriculture, and a Nutrition Council has been established to advise Ministry of Health in Ethiopia. Nutrition courses also have been introduced into the Public Health School in Gondar, Ethiopia.
9. An interdepartmental Committee on Nutrition has been established by Presidential decree in Vietnam and the Nutrition Laboratory established by ICNND in 1959 continues to receive strong support from the Ministry of Health.
10. Movie films of 30 to 45 minutes duration for nutrition education purposes have been prepared for Ethiopia and Vietnam and are in very active use in these countries as well as the United States. Similar films for Lebanon, Thailand, Chile, and Colombia are now in production and scheduled for completion in April 1962.

Direct Institute activities during fiscal year 1962

Research project grants.—The NIAMD supports research projects in foreign countries in three nutrition-connected general areas—malnutrition, metabolism, and anemia. A major portion of this support is concentrated in studies on protein mulnutrition, one of the most acute nutritional problems of the underdeveloped areas of the world. The Institute's earliest foreign grantee, the Institute of Nutrition for Central America and Panama (INCAP) has been an outstanding pioneer in studies on kwashiorkor (a prominent and frequently fatal protein deficiency disease of young children of worldwide distribution) and its effective treatment. One important result of this support has been the development of a mixed vegetable protein food formula based on indigenous agricultural products, which has proved extremely valuable in preventing and treating the disease.

A similar development of a dietary supplement to prevent infant malnutrition, based on locally produced agricultural products, is now being attempted in Peru under NIAMD grant support. Institute-supported studies in infant malnutrition are also being conducted in Mexico, Ecuador, Guatemala, Nigeria, the Congo, and South Africa.

Other studies are supported by NIAMD on the metabolic role of nutritional iron overload and its clinical consequences by investigators at the University of Natal, South Africa.

NIAMD also supports studies at the germ-free laboratory of the University of Lund, in Sweden, in the field of nutrition and intermediary metabolism.

This year, a major NIAMD grant has initiated a broad nutrition program in Lebanon in the form of a cooperative project between Columbia University's Institute of Nutrition Sciences and the American University of Beirut. This project is designed to improve public health nutrition education in Lebanon, provide research training for both Lebanese and U.S. students, initiate an exchange of faculty members, provide answers to problems of changing food habits, observe public health benefits of improved food nutrition, determine the chemical composition of indigenous foods, and study the incidence of riboflavin deficiency and goiter. As part of the project, a 4-year course in nutrition, leading to a B.S. degree, has been established at the American University of Beirut.

Another major research project is supported by the NIAMD in Indonesia and Thailand. The grantee scientists are presently conducting a pilot nutrition survey in selected areas of Indonesia and has instituted a pilot study for treatment of vitamin A deficiency with locally available red palm oil, in view of the high incidence of blindness due to a prevalent vitamin A deficiency in infants and children. In all, the grantee has planned five separate and diverse research projects for Indonesia. Under the same grant, three additional projects will be initiated in Thailand. The first project will be a dietetic survey, the second project will determine the thiamine content of breast milk as a possible index to the prevalence of infantile beriberi, and the third project will deal with the high incidence of a unique type of bladder and kidney stones which appear to be nutrition connected and which are found frequently in local children up to 10 years of age.

Direct collaborative studies.—The NIAMD has engaged in a number of international collaborative nutrition projects which have sent staff members to foreign countries and brought foreign scientists to Bethesda. The Institute has also furnished NIAMD staff members to serve as project officers for a number of Public Law 480 fund supported projects.

At the present time, one collaborative study concerns the possible role of selenium in kwashiorkor. This investigation has been centered in Jamaica and South Africa in the past, and plans are now underway for a similar project in Guatemala. In connection with this work, the NIAMD investigator is collaborating extensively with the Chemical Institute of Uppsala, Sweden, for preparation of special purified compounds of selenium needed in these experiments, and with other investigators in New Zealand where this nutritional factor is being used in the treatment of the economically very important, and locally endemic, muscular dystrophy in sheep.

At the request of Japanese sources, NIAMD scientists have participated in the elucidation of the cause of Minamata disease. This peculiar neurological disorder which emerged near Minamata Bay in Japan, has now been found to be due to industrial waste toxicity. The same scientists are presently engaged in a collaborative project intended to determine the effect of cycad nuts on experimental animals and the human liver. (The cycad nut is a hickory like nut which grows in Guam, which is consumed by the local population, and to which toxic effects have been ascribed.)

Foreign investigators from Turkey, Guatemala, India, England, and Italy have come to Bethesda for collaborative projects and training with NIAMD in nutritional techniques.

Other activities.—In addition to support of research projects and participation in collaborative studies, the NIAMD has supported a series of international conferences in the field of nutrition, the largest of which was the Fifth International Congress on Nutrition, held in Washington, D.C., in 1960. In addition to financial support by the Institute, staff members participated actively in the program of this conference which was attended by over 2,000 scientists from 65 nations.

Summary.—The National Institute of Arthritis and Metabolic Diseases has had a large and varied experience in the area of international nutrition. This has come about through the tradition of its component laboratories, through the interest and activities of its staff members, and through its partnership in the Interdepartmental Committee on Nutrition for National Defense. Efforts in international nutrition have been most fruitful during fiscal year 1962, not only in terms of new and productive scientific findings and valuable training of Institute and other American investigators, but also in terms of the good will engendered for the United States by the efforts of its nutrition scientists to bring improved nutrition and better health to a hungry world.

STUDIES ON GOUT

Mr. Fogarty. Give us a statement on your activities regarding gout and your collaborative studies.

(The requested information follows:)

Direct and Collaborative Studies on Gout

During the last year, studies carried out by National Institute of Arthritis and Metabolic Diseases scientists resulted in significant contributions to the understanding and control of gout. The basic defect in gout is an abnormal accumulation of uric acid in blood and tissues, either due to a pathologically enhanced uric acid production or as the result of an impairment in its excretion by the kidney; we now know that either mechanism can account for the disease. Recently scientists in Bethesda have elucidated the exact mechanism responsible for the acute disabling attacks of gouty arthritis. They demonstrated that the injection of microscopic, needle-shaped sodium urate crystals into the joints of volunteers will produce typical gouty attacks characterized by an acute inflammatory reaction with pain, tenderness to pressure, redness, fluid accumulation, and a leukocyte response in the affected joints. These findings are in sharp contrast to the previously accepted belief that urate salts (which are known to deposit in tissues in gouty patients) are inert and have little to do with the acute painful attacks of this disabling disease.

In another series of experiments, Institute clinicians demonstrated the effectiveness of sulfinpyrazone, a compound related to an earlier antirheumatic drug, phenylbutazone, as an agent which promotes the rapid excretion of uric acid from the body. The uricosuric action of the new drug was shown to be more potent than that of probenecid which had been in use heretofore; moreover, the new drug has been proven effective in cases where patients did not respond to probenecid.

In the area of diagnosis of gout, Institute investigators discovered that through their tendency to block the elimination of uric acid by the kidney, salicylates (such as aspirin) may cause abnormally high blood uric acid levels. Since elevated blood uric acid levels are an important diagnostic indicator in gout, this may lead to mistaken diagnoses of gout in individuals with acute joint pain who have taken salicylates for alleviation of their pain before presenting themselves to a physician. (As an outgrowth of this new and practical diagnostic observation, clinicians at the National Institute of Arthritis and Metabolic Diseases were able to establish that several patients, presented to them as allegedly suffering from gout, were really victims of rheumatoid arthritis.)

The National Institute of Arthritis and Metabolic Diseases supports a large number of extramural studies on the subject of gout. Among the subjects studied are investigations of uric acid levels in children suffering from a number of diseases including gout, epidemiologic studies of blood uric acid levels in normal populations and correlations with clinical findings of gout, studies contrasting the synovial fluids in gout and rheumatoid arthritis, the relationship between renal diseases and high blood uric acid levels, normal and abnormal uric acid levels in man, renal transport of uric acid in normal man and in gout, and purine metabolism in gouty arthritis.

During the past year, Institute grantees at Hahnemann Medical College in Philadelphia were able to substantiate the elucidation of the exact mechanism responsible for the acute attacks of gouty arthritis by confirming that these attacks can be precipitated by the injection of sodium urate crystals into the joints of volunteers.

Also during the past year, Institute grantees at Mount Sinai Hospital in New York, have summarized the results of their investigation of the efficacy of colchicine in preventing recurrent gouty arthritis over a period of from 2 to 10 years in 208 patients selected because of a prior history of frequent and disabling attacks of acute gouty arthritis. At the hand of these investigators, using specific dosage schedules, the prophylactic use of colchicine proved not only extremely effective (responses were 74 percent excellent, 20 percent satisfactory, 6 percent unsatisfactory), but generally safe and devoid of untoward side effects.

Gout may indeed be looked upon as one form of arthritis which has yielded significant ground to a concentrated research attack and which has now become reasonably manageable.

CLINICAL RESEARCH CENTERS

Mr. Fogarty. What are you doing with regard to your clinical research centers? How many do you have?

Dr. Daft. Our clinical research centers have just gotten started. We awarded one of those last year, and so it was started in fiscal year 1961. There was only one started in that year.

There have been a few others started since.

Mr. Fogarty. Give us information for the record on the numbers and where they are and what they are doing.

(The information requested follows:)

Clinical Research Centers

The program to support specialized hospitals units as facilities for high-quality clinical research in metabolic and rheumatic diseases was begun during fiscal year 1961 with a single such grant. During the present year three additional clinical center grants have been awarded so that the total number of clinical research centers now supported by the National Institute of Arthritis and Metabolic Diseases is four.

The initial research unit in this program is one of the oldest and most distingushed metabolic research wards in the United States, Ward 4 of the Massachusetts General Hospital in Boston (affiliated with Harvard University). This 10-bed unit, which had been in operation for 35 years, had been, in recent years, very inadequately supported resulting in curtailment of or inability to carry out a number of potentially important clinical research studies. Award of this National Institute of Arthritis and Metabolic Diseases grant, therefore, far from displacing other means of support, fulfilled an urgent need and has made possible continuation of metabolic research at this outstanding institution. In the past this research unit had enabled classical observations on the pathologic physiology of hyperparathyroidism, hyperthyroidism, Cushing's syndrome, rheumatoid arthritis, and ulcerative colitis. In the future similarly important studies may be expected in these and other diseases of particular interest to this Institute.

Work is currently being pursued on the Massachusetts General Hospital unit on such problems as: in rheumatoid arthritis, the structure and chemical characterization of collagen, amino sugar, glycoprotein and other vital components of connective tissue, the biology of agents which may be causally implicated in connective tissue diseases, and a study of the physiologic changes underlying various rheumatic diseases; in diabetes, development of methods of assay of serum insulin and of insulin-binding proteins, effect of oral drug treatment on diabetic complications and biochemical changes in fat tissue in diabetic patients with precocious atherosclerosis; in endocrinology, the effects of various hormones on protein synthesis and the relationship of steroid structure to physiologic action among various adrenal cortical hormones; and in gastroenterology, the metabolic and enzymatic changes in intestinal mucosa cells in various intestinal diseases.

The second institution now receiving clinical research unit support is the Robert Breck Brigham Hospital in Boston (also affiliated with Harvard), where metabolic studies are being carried on which are particularly devoted to intensified observations in arthritis. Investigations on this eight-bed unit include studies of the pathogenesis of the inflammatory lesion in arthritis and mechanism of action of anti-inflammatory agents; relationship of protein and antibody production, including detailed analysis of rheumatoid factors and their relationship to diagnosis and clinical classification of disease; metabolism of cartilage and bone, including investigation of the synthesis of cartilage mucopolysaccharides and of metabolic influences as kidney stone formation in diseases involving disuse and chronic disability, such as rheumatoid arthritis.

The third clinical research unit has been established at the West Virginia Medical Center in Morgantown. On a planned 10-bed unit members of the departments of Medicine and Surgery will study such varied metabolic problems as the interrelationships of adrenal cortical and ovarian steroids to water and electrolyte metabolism following injury and surgery; the relationship of the metabolism of magnesium to that of other elements in various diseases where it might play a critical role such as in thyroid, kidney and bone diseases and in cirrhosis of the liver; and various endocrinal, pulmonary and other physiological influences of obesity.

A small grant has been awarded to the Presbyterian-St. Luke's Hospital in Chicago for partial support of a special two-bed clinical unit which will be used primarily for metabolic balance studies of various aspects of bone and thyroid diseases and of diabetes where precise control of food intake and excretory output are necessary to determine the behavior of key elements.

Clinical research centers of this specialized type support project research in a very useful and effective way by providing the highly controlled research environment essential to the success of certain important metabolic and rheumatic disease studies.

Mr. FOGARTY. Is there anything else you would like to say?

Dr. DAFT. No, sir. Thank you very much.

Mr. FOGARTY. Thank you very much.

We will reconvene at 1:30.

(The following was submitted for the record at the request of the committee:)

DEATHS, DISABILITY AND COST OF ARTHRITIS AND METABOLIC DISEASE

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, PUBLIC HEALTH SERVICE

ARTHRITIS AND METABOLIC DISEASE ACTIVITIES

Statistics concerning the annual number of deaths and total current number of disabilities caused by some of the major diseases under study in the National Institute of Arthritis and Metabolic Diseases and the estimated annual cost to the Nation:

I. Deaths during 1960 (National Office of Vital Statistics):	
Category:	
Diabetes mellitus	30,790
Gastrointestinal diseases (ulcer of stomach and duodenum, and cirrhosis of the liver)	31,030
Total	61,820
II. Disabilities (National Health Education Committee, Inc.—1961): Rheumatic diseases (243,000 persons completely disabled and 1,670,000 persons partially disabled)	1,913,000
III. Estimated annual economic cost to the Nation (National Health Education Committee, Inc, 1961): Rheumatic diseases (arthritis, rheumatism, gout)	$2,000,000,000

HIGHLIGHTS OF PROGRESS IN RESEARCH ON ARTHRITIS AND METABOLIC DISEASES, 1961

HIGHLIGHTS OF RESEARCH PROGRESS—THE SECOND DECADE

The year 1961 marks the entrance of the National Institute of Arthritis and Metabolic Diseases (NIAMD) into its second decade of laboratory and clinical research. This decade has already been distinguished by many important advances, both by Institute scientists and by those in the many non-Government research centers receiving financial support from the Institute. The wide scope of their findings—from the partial cracking of the important genetic code to the use of combinations of new and old drugs to control diabetes—reflects the broad clinical and basic research interests of the Institute.

Another result, however, underlies all of these research findings; one of the important things which scientists learn by research in the method and means to find out more. Their findings, revealing in themselves, also serve as precursors for even more exciting discoveries to come.

The following highlights of research are presented in nontechnical language and categorized under various disease headings for the convenience of the reader.

RHEUMATIC DISEASES

The milestones that mark the Institute's efforts to combat the rheumatic diseases are becoming more frequent. Current research aimed at coping with these diseases is in sharp contrast with the period a comparatively few short years ago when little or nothing was being done to study rheumatoid arthritis, osteoarthritis, gout, and other rheumatic diseases. A case in point is the ancient disease, gout. Institute-supported scientists during the past year have shown that the use of a combination of certain new and old drugs can make gout one of the best-controlled forms of arthritis. Recent efforts directed at uncovering the environmental and genetic aspects of rheumatic diseases promise to provide much needed basic information about the cause of these disorders. The concept that some of the rheumatic diseases may be caused by hypersensitivity, that is, abnormal sensitivity by rheumatic patients to their own tissue proteins, have been further strengthened by recent studies in both animals and man.

High calcium diet protects against certain corticosteroid effects

NIAMD scientists have found that increasing dietary calcium in patients with osteoporosis may support and protect the skeleton from further weakening associated with corticosteroid therapy for arthritis. These studies may lead to a fuller understanding of the "bone thinning" mechanism of osteoporosis, a disease characterized by demineralization and loss of calcium.

Recent surveys indicate that osteoporosis of the spine affects 30 percent of postmenopausal women, and is probably more common in older women with rheumatoid arthritis. Clinical experience has indicated that the synthetic, anti-inflammatory corticosteroid hormones given to osteoporotic patients for relief of arthritis tend to bring about vertebral and rib fractures. The mechanism for this harmful effect has not been clear, although excessive calcium loss from the body has been suggested.

To investigate the effects of corticosteroids, Dr. G. Donald Whedon, Dr. Leo Lutwak, and Preston Smith, of NIAMD, have performed 13 calcium balance studies in 11 patients receiving 5 different corticosteroid preparations. They found that under the influence of corticosteroids calcium balance became negative in eight studies, positive in three, and remained unchanged in two. Despite the varying response among patients, the results of the studies generally support the belief that corticosteroid administration causes calcium loss.

Some physicians have suggested the use of gonadal steroid hormones to prevent or decrease this mineral loss induced by corticosteroids, but the Institute investigators found that androgen and estrogen combined were unable to promote calcium storage in two arthritic patients so treated.

In two other studies, however, significant calcium storage was produced during cortiscosteroid administration by increasing the dietary calcium intake to high levels. Additionally, high calcium diets given to seven patients with postmenopausal osteoporosis who were not receiving corticosteroids not only prevented calcium loss in six of the patients but also enabled four of them to begin storing calcium. This suggests that high calcium diet may have a protective value to the skeleton, although a complexity of factors appear to be involved in regulating calcium utilization.

The scientists reported that they have found no supporting evidence for the belief that high calcium intakes may be harmful; on the contrary, their studies indicate that calcium requirements vary among individuals and are probably higher than normal in individuals who develop osteoporosis. They suggest that high calcium diet is currently the most reasonable clinical management procedure to protect against the skeletal effects of corticosteroid treatment.

Unusually high frequency of connective tissue disease in agammaglobulinemia patients

NIAMD-supported investigators have found a surprisingly high frequency of connective tissue diseases in patients with agammaglobulinemia. This observation is of considerable theoretical interest in view of current evidence that immunologic mechanisms are related to the cause of these diseases, including rheumatoid arthritis.

In the past several years, major research activity in the rheumatic disease field has centered on the immunologic mechanisms operating in the arthritic disorders. During the past 6 years, the investigators, Drs. Jerome Rotstein and Robert Good, Montefiore Hospital, New York, and the University of Minnesota, have studied 41 patients with agammaglobulinemia, some with the congenital form and others with the acquired form of the disease. All had the classical signs—inability to produce plasma cells, gammaglobulin, and circulating antibody. (These antibodies are responsible for immediate immune reactions in contrast to delayed immune reactions. Agammaglobulinemic patients are capable of producing delayed hypersensitivity response.)

Notably, one-third of the patients were found to suffer from connective tissue disease such as rheumatoid arthritis, lupus-like syndrome, and scleroderma. "This surprising frequency seems too high for a coincidental finding in view of the known incidence of these diseases in the general population," the physicians reported.

The finding of the investigators is of considerable theoretical interest, especially in view of the steadily mounting evidence that one or another type of immunologic reaction is linked to the basic cause of these diseases. "In such a situation, the connective tissue disease may represent a direct response to the host to the infecting agent, a hypersensitivity reaction to the agent in which mechanisms of delayed allergy are operative, or a response to the agent of another type of cellular hypersensitivity similar, but not identical, to delayed allergy," they reported.

Arthritis in rats produced by injections of Freund's adjuvant

A technique for producing experimental arthritis in rats by using multiple injections of Freund's adjuvant over a long period of time has been reported by an NIAMD grantee. Freund's adjuvant is an extract of killed tubercle bacilli in an oil and water medium that is often used to induce or enhance immune reactions. The work may lead to a more satisfactory laboratory model of the disease to aid further research and indicates the close involvement of immune mechanisms.

Dr. Carl M. Pearson of the University of California Medical Center, Los Angeles, reported on detailed studies made of the arthritis produced by the adjuvant. All stages of the disease were studied, from clinical onset to the 350th postinoculation day and joint changes were carefully noted. The adjuvant arthritis bears a number of similarities to human rheumatoid arthritis: joint inflammation and exudation in the acute stage; connective tissue invasion of the underlying bone, sometimes extending over the articular cartilage; and a continuing active inflammatory process in some animals for many months.

"It is concluded that from a pathologic viewpoint the lesions are those of an acute arthritis and spondylitis which proceeds to a chronic phase with persistent activity in some animals," the NIAMD grantee reported.

The adjuvant technique provides a means for producing an experimental arthritis which is caused not by invasion of detectable microbial agents but seems to be related to a delayed hypersensitivity reaction.

Complement levels aid diagnosis of certain kidney diseases

Institute grantees have found a marked lowering of serum complement levels in 245 of 246 cases of acute glomerulonephritis and in 75 percent of disseminated lupus erythematosus cases. The complement reduction, believed caused by a complement-binding, antigen-antibody reaction, has practical diagnostic value and perhaps some etiologic significance.

A normal constituent of serum, the complement system is known to aid removal of foreign or toxic substances previously neutralized by antibody. During acute stages of some diseases serum complement shows an increase which tends to return to normal with recovery, while in other diseases the level falls before returning. Why the alteration in level differs has not been determined.

In their work, part of a 10-year study of complement level in 3,051 patients with various kidney diseases, the NIAMD grantees used originally devised procedures to determine whether diagnosis and prognosis can be made on the basis of complement level in acute glomerulonephritis—a disease characterized by inflammation of kidney glomeruli.

The sera of 246 patients with acute glomerulonephritis were examined and all cases except one showed a marked reduction of complement. The average initial complement value was 0.49 unit, or about one-fifth of normal average. Low levels were not seen in sera from nonglomerulonephritic patients having signs, such as hematuria, which may masquerade as the disease. In the first and largest group, the complement remained low for several weeks before returning to normal, coincident with a gradual clearing of the disease. The level in a second group showed no return and all patients in this study died of uremia within 4 years, indicating that continued low levels offer a poor prognosis. In a third group representing patients with chronic glomerulonephritis, the level was normal.

The scientists also confirmed earlier findings of a complement reduction in cases of disseminated lupus erythematosus, apparently related to rheumatoid arthritis. Since arthritis has either a normal- or high-complement level, the scientists believe complement examination may serve to differentiate the two diseases. Discrimination may also be made between pure nephrosis (degenerative kidney lesions), in which the level was found lowered in 85 percent of the cases studied, and other nephrotic syndromes, where complement was normal.

Drs. Kurt Lange, Edward Wassermen, and Lawrence Slobody of the New York Medical College, suggest that their work strengthens their earlier hypothesis that an antigen-antibody reaction may tend to bind complement in these diseases and provides further insight into the basic mechanism of these diseases. The study was reported in the "Annals of Internal Medicine."

Genetic predisposition to Sjogren's syndrome suggested

A family study of patients with Sjogren's syndrome, a disorder often accompanied by rheumatoid arthritis, has shown that normal blood relatives of patients often have a variety of occult or ignored manifestations of the disease, suggesting a genetic predisposition.

Previous investigations by NIAMD scientists have shown that patients with Sjogren's syndrome have a high frequency of abnormal circulating antibodies. Since it is known that blood relatives of patients with some rheumatic diseases have a high frequency of abnormal antibodies, the investigators sought to determine whether relatives of Sjogren patients also exhibited this frequency.

Fourteen families of Sjogren patients totaling 166 relatives and nine families of controls totaling 72 relatives were examined by Drs. Joseph J. Bunim and Thomas A. Burch of the Institute's Arthritis and Rheumatism Branch. The controls were neighbors of the patients, and were of the same age, sex, and ethnic background. All of the subjects were divided into three groups: the first contained those immediately related (parents, siblings, and children) ; the second, other relatives; and the third, all controls and their relatives.

Serological manifestations such as the presence of rheumatoid factor, abnormal antibodies and antinuclear factor, and high gamma globulin concentrations were investigated and combined with symptoms of rheumatic complaints, and then checked against the diagnostic criteria of the American Rheumatism Association which indicate classical, definite, or probable rheumatoid arthritis.

The NIAMD investigators found that 17 percent of the first group met two or more of the criteria in contrast to 5 percent of the second group, and 2.5 percent of the third. The Schrimer's test for eye dryness (Sjogren's syndrome is characterized by hypofunctioning of both the tear and salivary glands) was positive for 30 percent of the first group, 15 percent of the second, and 5 percent of the third. Other tests involving abnormal elevation of gamma globulin and the presence of abnormal circulating antibodies, yielded similar results.

These findings suggest that a genetic mechanism is operative in the disease. i.e., the full genetic endowment probably leads to the frank disease with all its characteristics while a partial genetic endowment may result in only partial manifestations among blood relatives.

Environment may be linked to rheumatoid arthritis cause

A study by NIAMD grantees has shown for the first time that husbands and wives of patients with rheumatoid arthritis often had clinical symptoms and blood changes typical of the disease, thus suggesting the involvement of some common environmental factors in the close contact of family life in the cause of the disease, as well as previously suspected genetic factors. This preliminary study of more than 450 persons also confirmed earlier findings of the high incidence of the disease's manifestations in blood relatives of patients.

The investigators, Dr. Frank R. Schmid and his associates at Northwestern University, Evanston, Ill., found, among other symptoms and signs in the spouses, abnormal concentrations of gamma globulin and the rheumatoid factor—indications of the body's protective mechanism against the disease.

Griseofulvin effective against gout

Dramatic results in the treatment of acute gouty arthritis without undesirable side effects have been obtained with the new fungistatic antibiotic, griseofulvin, by NIAMD-supported investigators at the University of Miami School of Medicine. In a series of 23 attacks in 22 patients complete remission of symptoms was obtained within 48 hours of treatment in 14 patients and moderate improvement of 5 others within 24 hours.

The investigators were led to try griseofulvin because its structural formula resembled that of colchicine and, like colchicine, it interferes with purine metabolism and cell division. Colchicine is currently the most effective agent for relieving the painful attacks of gouty arthritis. Despite its effectiveness, however, it produces distressing side effects such as nausea, vomiting, and diarrhea which limit its usefulness. Thus, many investigators have been searching for analogs of colchicine which might be more safely applicable.

Drs. Roberte Slonim, David S. Howell, and Harvey E. Brown, Jr., reported that stiffness, pain, erythema, swelling and heat decreased greatly or disappeared during treatment with 4 to 12 grams of griseofulvin administered over a 48 hour period. There were no definite toxic reactions. The only signs of presumed toxicity were found in six patients who had been vomiting before treatment was initiated, and who continued to do so thereafter. A generalized rash which appeared on one patient after therapy did not reappear during treatment for a second attack. Patients resistant to griseofulvin were also resistant to colchicine.

Although the series was too small to exclude completely the possibility that griseofulvin could be acting merely to subdue to reduce inflamation or fever, the investigators found no basis for postulating such an effect. In the patients studied, no evidence of uricosuric action was found. There was no significant effect on serum uric acid levels after 48 hours treatment; and, except in two patients whose gout was in the early stages, the serum uric acid levels were elevated.

The effectiveness of the new compound suggests means of learning more exactly the mode of action of these agents. If the antiarthritic response is produced by colchicine and griseofulvin at the same biochemical sites, certain similarity of their chemical structure may provide a clue to the active groups.

Gout-like response produced by injection of urate crystals into a joint

Drs. R. Rodney Howell and J. E. Seegmiller of NIAMD's Arthritis and Rheumatism Branch have found that injections of needle-shaped microscopic sodium urate crystals will produce an inflamatory reaction when injected into the joints of gout patients. The reactions, which were produced in volunteer patients, were similar to those found in attacks of acute gouty arthritis. They were characterized by pain, warmth, tenderness, redness, fluid accumulation and a leukocytic (white cell) response in joint fluid. Inflammation was not produced, however, by injections of either sodium urate solution or a suspension of amorphorus sodium urate.

The work of the NIAMD scientists holds promise for discovery of a long-sought-after link between the two main features of gout: the painful, recurring attacks which are the first indication that a patient has gout; and the inherited defect in body chemistry which leads to an accumulation of uric acid within the body.

In addition to injecting the crystals into volunteer gout patients; the Institute scientists also injected them into the skin of normal people. Here, too, they produced inflammatory reactions. In related studies in animals, preliminary results indicate that the injected needle-shaped crystals can bring about attacks of acute gout-like arthritis in normal joints.

From these observations, the NIAMD scientists concluded that certain forms of crystalline sodium urate may be directly involved in the cause of some aspects of acute gouty arthiritis. This concept is in sharp contrast to the accepted belief that urate salts are inert substances and have little or nothing to do with the acute painful attacks of gout.

Salicylates may cause wrong diagnosis of gout

NIAMD scientists have reported that the urate-retaining effect of low doses of salicylate can result in the wrong diagnosis of gout in some patients with joint pains. High blood levels of uric acid (serum urate) are associated with gout and may lead to the buildup of urate deposits, or tophi, in and around the joints of some patients. To prevent tophi from forming and impairing joint motion, gout patients are given drugs such as probenecid to increase the elimination of uric acid and lower serum urate levels.

Recently, two persons with joint pains and high serum urate levels were referred to NIAMD when they failed to respond to colchicine, the traditional remedy for gout attacks. Institute scientists found that the high blood levels of uric acid had been caused not by gout, but by diminished urinary excretion of urate induced by low doses of aspirin which the patients had taken to relive their pains.

The scientists reported that the two cases, now rediagnosed as rheumatoid arthritis, point up a poorly known side effect of salicylate which should be taken into account when diagnosing questionable cases of gout. Low doses of salicylate cause abnormally high levels of serum urate, probably because the drug acts by blocking secretion by the kidneys. Paradoxically, large doses of salicylate are known to increase urate elimination.

To determine just how significant blood levels of uric acid are in diagnosing gout, the scientists measured these levels in a variety of individuals. Their findings indicate that as many as 12 percent of normal men and 10 percent of normal women could be expected to have levels above what is commonly considered to be the dividing point between normal and gout levels, according to a method of determination in common use. In order for serum urate levels to be of more diagnostic help to physicians, this dividing point may need to be raised when this particular method of determination is used.

Studies of the effects of varying doses of salicylate showed that four aspirin tablets a day (1.2 gms. of salicylate) could cause the serum urate level of almost all normal males to rise. A similar effect occurred in most gout patients, where moderate doses of salicylate caused varying degrees of urate retention.

Aspirin is also detrimental in certain gout patients, since it inhibits the action of some of the newer uricosuric drugs used to increase urate elimination. Because of these side effects the researchers believe that acetaminophen, an analgesic compound which lacks urate-retaining effects, should be used in place of aspirin. The NIAMD scientists were Dr. A. I. Grayzel, L. Liddle, and Dr. J. E. Seegmiller.

DIABETES

Research in diabetes, probably the best known and most important of the metabolic diseases, is undergoing a new wave of interest, stimulated by the dramatic effects of oral antidiabetic drugs. Much of this interest stems from the fact that although these drugs are widely used, the way they lower the high blood sugar levels of the disease is still not fully understood. Continuing clinical studies during the past year with the oral drugs have shown that combinations of them are effective in controlling diabetes in a number of patients who are not helped by single drugs alone.

Improved diabetes control possible with oral drug combination

A more efficacious method of oral therapy for stable (ketoacidosis-resistant) diabetic patients has been reported by two NIAMD grantees. The combinations of a sulfonylurea drug with phenformin (DBI)—in smaller doses than those required to obtain an antidiabetic effect when each drug is used alone—avoids the therapeutic failures of single drug therapy, provides better control for a large number of diabetics previously unresponsive to oral therapy, and compared to therapy with a single oral drug enjoys a wider margin of safety with considerably reduced side effects.

Tolbutamide, when effective in maintaining normal blood sugar levels, may be the drug of choice in the adult, stable, ketoacidosis-resistant form of diabetes. However, since tolbutamide fails to achieve or to maintain the desired blood glucose levels in a substantial proportion of this group of patients the need exists for other forms of oral therapy capable of maintaining effective control.

Two other currently available oral hypoglycemic drugs, chlorpropamide and phenformin may be effective in a minority of such cases. Chlorpropamide is a more potent and longer acting sulfonylurea than tolbutamide. Although a small percentage of tolbutamide-resistant patients may respond to chlorpropamide, its use entails a small but definite risk of toxic side effects and hypoglycemic reactions. Phenformin differs from the above two sulfonylurea drugs in its chemical structure and mechanisms of action.

Dr. S. B. Beaser of Harvard Medical School and Dr. R. H. Unger and associates of the VA Hospital and Southwestern Medical School in Dallas, have reported independently on successful sulfonylurea-phenformin combination therapy. In the first series, out of 25 diabetic patients refractory to treatment with a sulfonylurea drug alone, combination therapy was successful in 19 patients. In the second series, a group of 80 patients who had been inadequately regulated by a single oral drug were given prolonged tolbutamide-phenformin treatment. This regimen brought about significant improvement or control in 70 percent of patients previously uncontrolled by tolbutamide alone and in 60 percent previously uncontrolled by phenformin alone. The NIAMD-supported investigators conclude that apparently the combination of the two classes of drugs is additive with respect to their hypoglycemic action but not with respect to their side effects, and that this method of combination therapy makes adequate control with oral drugs a practical possibility for most stable diabetics in whom single oral agents have heretofore been unsuccessful.

Unique lesion of small blood vessels found in diabetics

NIAMD grantees have found a unique lesion of small blood vessels in diabetics which appears to be related to an immunologic process. The newly found lesion is characterized by endothelial proliferation in the blood vessels and has been seen in the small arteries and capillaries in gangrenous extremities, in myocardium, retina, and occasionally, in the placental veins of diabetic patients.

Discovery of the lesion stemmed from a study of the relationship between diabetes mellitus and various types of lesions associated with vascular complications, which present a most serious problem in the management of diabetes.

From these and earlier studies the institute grantees doubt that there is any important difference in the incidence of atherosclerosis in diabetics and nondiabetics when age and other factors are properly considered. In attempting to account on some other basis for diabetic vascular complications, the investigators found the unusual lesions in smaller vessels than those usually affected by atherosclerosis. The lesion contains no fatty substances and differs from atherosclerotic patches by virtue of a characteristic mucopolysaccharidic substance surrounding the endothelial cells; there are also major differences in the involvement of the vascular muscle wall and elastic membrane. The proliferative lesion has been previously identified in the placentas of nondiabetic women who have had incompatible Rh-negative infants and in association with glomerulonephritis, multiple myeloma, rheumatic fever, and rheumatoid arthritis.

In an earlier study the same investigators reported finding similar proliferative lesions in the intramural coronary artery branches of diabetics. The lesions were found more than twice as frequently among diabetics as among nondiabetics and might explain the diabetic patients' difficulty in establishing adequate collateral circulation after a myocardial infarction.

Since the lesions resemble those which have been produced experimentally by a variety of immunogenic mechanisms, and since giant cells and plasma cell and round cell infiltration with fibrinoid degeneration have also been found, the NIAMD grantees believe that hyperimmunity may be a factor in diabetic vascular disease. Further studies are being carried out to determine what immunologic reactions may be taking place.

The studies were conducted by Drs. Herman T. Blumenthal, Morris Alex, and Sidney Goldenberg, of St. Louis, Mo.

Hormones necessary for ketosis development identified

Institute scientists have found that ACTH is the hormone of the anterior pituitary gland necessary for development of ketosis in insulin-deficient rats. This further implication of the pituitary may lead to a better understanding of the sudden and apparently uncontrollable ketosis which develops in some diabetic patients.

Previous studies by other investigators in experimental diabetes have demonstrated that both the anterior pituitary and adrenal glands are necessary for fat mobilization and ketosis in the diabetic animal. However, the specific hormones involved and their site and mode of action had not been identified.

Drs. Robert O. Scow and Sidney S. Chernick, of NIAMD's Laboratory of Nutrition and Endocrinology, studied the effects of varying amounts of insulin and of other hormones on the increasing levels of sugar, ketone bodies, and fats in the blood of pancreatectomized rats. Removal of 99.5 percent of the pancreas was made possible by Dr. Scow who had developed new delicate surgical techniques, employing a microscope and miniature instruments.

The investigators found that pituitary adrenocorticotrophic hormone (ACTH) had no effect in raising blood sugar and ketone bodies when the adrenals were removed from the animal. However, a significant rise was observed when the adrenals were intact. This demonstrates that the ketosis-forming action of ACTH is mediated through the adrenal cortex, in all probability by stimulating secretion of glucocorticoids—hormones from the cortex which affect the rise of blood-sugar. Growth hormone, another hormone of the pituitary, had very little ketosis-forming action, even when given with small doses of glucocorticoids.

The Institute scientists also reported that the accumulation of fat in the liver results in an increase in the formation of ketone bodies. Insulin was found to have no effect on this formation in the liver, but did accelerate removal of ketone bodies from the blood.

Chromium linked to insulin action in rats

NIAMD scientists have demonstrated a direct action of chromium (III) in maintaining normal glucose utilization in rats. In vitro studies on rat fat tissue indicate that chromium is intimately related to the action of insulin in the animal body.

Previous work by Drs. Klaus Schwarz and Walter Mertz of the Laboratory of Nutrition and Endocrinology identified chromium (III) as the active ingredient of the glucose tolerance factor (GTF), a dietary agent necessary in rats for the normal utilization of glucose. Rats raised on GTF-deficient diets were found to have a reduced rate of removal of intravenously injected glucose. However, when exceedingly small amounts of active chromium were given to the animals, the removal rate was restored to the normal control value.

Since intravenous glucose tolerance is affected by many regulatory mechanisms in the intact animal, the Institute scientists have now completed in vitro studies with epididymal fat tissue to define the site of action of GTF more closely. These tissue preparations, of approximately 100 milligrams each, were taken from animals on GTF-deficient and supplemented diets, respectively.

The studies have shown that chromium causes an 80 to 100 percent increase of glucose uptake by fat tissue from GTF-deficient rats. This increase was seen only in the presence of insulin. An optimum effect was obtained when as little as 1 in 100 microgram of chromium was supplied, along with minute amounts of insulin. Identical conclusions could be reached from studies in which radioactively labeled glucose was used for measuring the amount of glucose converted into fat. (A major metabolic pathway for the excess glucose administered during the course of a glucose tolerance test is conversion into fat.) Amounts of chromium found to be effective are of an order of magnitude similar to those present in nutrients and in body tissues.

This direct evidence of chromium's role in glucose utilization opens up a great number of interesting questions. The data available from the studies give no indication as to the site of action of chromium in the metabolic process, but they show that the chromium effect depends on the presence of insulin. The investigators believe it is possible, mutatis mutandis, that insulin depends for its action on the presence of very small amounts of chromium. The in vitro work was reported by Drs. Mertz, Edward E. Roginski, and Schwarz in the Journal of Biological Chemistry.

Glucagon may regulate plasma lipids

Evidence that the alpha cells of the pancreas secrete glucagon, that they are the sole intrinsic source of it, and that glucagon is an important factor in regulating the level of fatty substances in the blood has been presented by NIAMD grantees, Dr. Edward Paloyan and Paul V. Harper, Jr., of the University of Chicago, in a report in Metabolism.

The evidence was obtained from studies of dogs in which the pancreas was surgically transformed into three distinct glands:

1. An exocrine gland supplying pancreatic juice to the bowel;
2. An endocrine gland containing beta cells (source of insulin); and
3. An endocrine gland containing both beta cells and alpha cells.

These transformations were possible because of the peculiar natural distribution of alpha and beta cells in various parts of the organ.

Marked hyperlipemia (excess of fatty substances in the blood) occurred in the animals from whom the portion of the pancreas containing the alpha cells was removed. No such hyperlipemia occurred when the portion of pancreas containing the alpha cells remained intact.

In the animals with hyperlipemia, injections of glucagon lowered the lipid level strikingly within 48 hours. With discontinuation of the glucagon injections, the lipid level rose gradually.

Further studies are needed, the scientists point out, to learn that biochemical mechanism of the action of glucagon in relation to lipid metabolism.

Long-term tolbutamide feeding may prevent pancreatic deterioration in rats

NIAMD grantees have reported that feeding of tolbutamide for 12 to 15 months to rats made "subdiabetic" by alloxan did not cause deterioration in pancreatic function beyond that caused by alloxan alone. On the contrary both histologic and physiologic evidence suggest that administration of tolbutamide to maintain normal blood sugar levels may even result in some improvement.

One of the reasons for the blood-sugar-lowering effect of sulfonylureas such as tolbutamide is believed to be the release of insulin from the pancreas. It is not known, however, what long-term effects this stimulation might have on the insulin-producing beta cells. It has been feared that beta cell exhaustion, leading to further impairment of the basic endocrinologic defect in diabetes, might occur. If so, this might be of serious consequence to thousands of patients with mild diabetes now receiving tolbutamide and the other oral antidiabetic drugs.

In order to determine whether as the result of tolbutamide administration any significant changes in pancreatic function could be detected, as evidenced by either an improvement in glucose tolerance on the one hand or by the appearance of frank diabetes on the other, the grantees studied rats made subdiabetic with alloxan—a pancreas-destroying drug used to produce varying degrees of experimental diabetes. All of the animals used exhibited no urinary sugar (glycosuria) but had abnormal glucose tolerance. During the 15-month study period, an experimental group of rats was fed a diet containing 2 percent of tolbutamide while a control group was not. The investigators, Drs. Jann W. Weber, Piero P. Foa and associates at the Chicago Medical School, Chicago, found that after several months glucose tolerance became significantly better in the tolbutamide-fed animals whereas in the alloxan-subdiabetic controls glucose tolerance became gradually poorer; in the rats of the tolbutamide series whenever glucose tolerance tests were performed, the oral drug was discontinued for 3 days in advance in order to avoid any immediate effects of the drug. They also found that the islets of Langerhans in the controls showed marked degranulation of the beta cells while those of the tolbutamide-fed rats appeared normal.

OTHER METABOLIC DISORDERS

Encouraging results reported in treatment of Wilson's disease

NIAMD grantees have developed a therapeutic and preventive regimen for Wilson's disease that has produced encouraging results. In a group of five patients with this grave metabolic disorder there was definite clinical improvement seen in four and probable improvement in the fifth after treatment for from 3 to 5 years. A sixth patient, treated since the age of 10 months, was a 5-year-old boy who would have developed the disease if left untreated.

Wilson's disease, a rare familial illness, is caused by the body's inability to limit the absorption of copper from the diet and/or excrete copper already absorbed. Toxic deposits of the metal accumulate in the tissues and are believed to cause the damage to the central nervous system, kidney, and liver, and the greenish corneal pigmentation that are characteristic of the disorder.

From their 5-year study, the NIAMD grantees have developed a basic regimen which makes use of several types of therapy which have been employed by other investigators.

The regimen has a twofold purpose: to diminish the absorption of dietary copper and promote urinary excretion of the metal from the body. Absorption is reduced by feeding a copper-poor diet plus 20 milligrams of potassium sulfide with each meal to remove whatever copper is still present in the food. Urinary excretion is promoted by the administration of penicillamine (a metal-binding agent), given in divided doses on an empty stomach.

Although results are difficult to evaluate because of the disease's insidious character, lessening of such neurological symptoms as tremors, and the fading or disappearance of corneal pigmentation (Kayser-Fleischer rings) have been the most noteworthy effects. However there was no improvement in liver function. The greatest value of the treatment should be in infants and children who have been diagnosed as having Wilson's disease but who have not yet shown any symptoms and who are presumed to be still free of irreversible toxic damage. In these cases, the grantees believe, the treatment may be able to delay or prevent the development of the full-blown disease picture.

The NIAMD grantees, Drs. I. Herbert Scheinberg and Irmin Sternlieb, of New York City, have commented that the described treatment is more effective and practical than therapy utilizing BAL or versene alone.

Evidence of acquired porphyria in man and rat provided

Institute-supported scientists have found that dietary preparations of hexachlorobenzene, a fungicidal agent, can produce porphyria in rats. This finding supports the suggestion that its ingestion caused the recent outbreak of the disease in Turkey, and represents direct experimental evidence of an acquired toxic form of porphyria.

The term "porphyria" embraces a group of uncommon diseases in which unusual symptoms involving the skin, abdominal organs, or nervous system are associated with urinary excretion of various forms of porphyrin. Porphyrins are chemical compounds which form part of the structure of hemogloblin and of other molecules necessary for metabolism in animals and plants. Although porphyria is regarded as an inborn error of metabolism, depending on an inherited constitutional abnormality, porphyria has occasionally occurred following prolonged use of a number of drugs, including barbiturates and sulfonamides. It has thus far been generally believed, however, that this effect occurs only in those individuals already having a latent inherited tendency to porphorinuria, because of the lack of convincing evidence of an acquired form of the disease.

Recently an outbreak of several thousand cases of cutaneous porphyria occurred in certain Provinces in Turkey. The patients exhibited symptoms and signs common to this form of the disease, such as enlargement of the liver, skin sensitivity to light and minor trauma, and skin blistering which in some cases developed into infected lesions giving rise to a suppurative arthritis and osteomelitis. The disease occurred in population groups which appear to be genetically distinct, domestic Turks, Kurds, and Turks repatriated after several centuries of residence in the Balkans.

Although dietary histories suggested that virtually all of the patients in this outbreak had consumed wheat treated with a fungicide, hexachlorobenzene, it was not possible to prove by dietary history alone that hexachlorobenzene had caused the disease. In view of this and conflicting toxiocological information on the fungicide, the investigators sought to determine whether chronic ingestion of hexachlorobenzene could result in a disturbance in porphyrin metabolism in animals.

In a group of 33 rats fed a diet containing 0.2 percent hexachlorobenzene, 13 died within the first month after exhibiting tremors, lack of muscle coordination (ataxia), weakness, and paralysis. There was no evidence in this group of faulty porphyrin metabolism. In the remaining 20 rats, a significant increase in urinary excretion of porphyrin precursors was noted in the first 2 to 8 weeks. Although a discontinuation of the diet showed a return to normal porphyrin metabolism in some cases, repeated feedings resulted in an irreversible porphyric state with neurological complications and increased excretions of various forms of porphyrin. Enlargement of the liver and degeneration of liver cells were found to be common.

The animal study findings, by Drs. Robert K. Ockner and Rudi Schmid, of the Harvard Medical School, coupled with the suggestive evidence that hexachlorobenzene accounted for the human cases of porphyria in Turkey, present the strongest evidence so far obtained for an acquired toxic form of porphyria. The study is also significant because of the indicated toxicological effects of compounds used for plant disease control and because it reemphasizes the importance to health of careful surveillance of food production methods.

Antibody to normal human serum protein shown

Clinical studies by NIAMD scientists have shown that antibodies to a normal human serum protein developed in five patients who were given multiple transfusions. This finding demonstrates further differences in human biochemical makeup and may provide an answer to unexplained posttransfusion reactions.

During the past few years the field of genetic blood characterization has developed in new directions due to the finding that people can be classified into sharply distinct groups according to differences in their serum proteins. Many of these serum protein variations are genetically determined and can be detected by starch gel electrophoresis and other techniques.

These developments prompted Institute scientists to investigate the possibility that serums of people who had received multiple blood transfusions might contain antibodies which would react with particular serum proteins, present in some individuals but not in others. Such a reaction had been shown in rabbits and monkeys by previous investigators.

The NIAMD scientists first found a precipitin (an antibody which acts on its antigen to produce a precipitate) in the serum of a patient who had received approximately 50 transfusions recently with such reactions as fever, headache, and muscle pain for no known reasons. There was no evidence of red cell incompatibility with donor bloods; rather the patient's serum gave a well-defined precipitin reaction (i.e., acted as an antibody) with an alpha-2 macroglobulin, a protein present in the serum of some normal individuals but not in the serum of others. The investigators subsequently found an antiprotein antibody in four other patients, two of whom seemed to have the same antibody as the first subject.

Family and twin studies of the precipitin reaction showed that the presence or absence of the alpha-2 globulin which causes precipitation with the transfused patient's antibody is inherited according to simple Mendelian rules. The gene which determines the presence of the protein in normal serum which reacts with antibody has been designated "Ag^A." Approximately half of the American serums tested by the NIAMD scientists contained the protein giving the precipitin reaction. In a sample of serums from a central Pacific Micronesian population 50 out of 51 individuals gave a positive precipitin reaction, indicating that the frequency of the antigen varies in different geographic groups.

Besides being of genetic and anthropological interest, this finding of a specific precipitin in serum suggests that human serum protein isoimmunization may occur. The studies by Drs. A. C. Allison (NIAMD visiting scientist, now at the National Institute for Medical Research, London) and B. S. Blumberg of NIAMD's Epidemiology and Biometry Branch, reported in the Lancet, also indicate that serum protein antigen-antibody reactions may be involved in some posttransfusion reactions in multitransfused patients.

Familial Mediterranean fever may be due to recessive gene

Results from genetic investigations by NIAMD grantees have shown that familial Mediterranean fever is due to a complete autosomal recessive gene. The grantees believe that the disease is a separate entity with sharp clinical characteristics.

Familial Mediterranean fever (FMF), or periodic fever, usually begins in childhood and is seen almost exclusively in individuals of Mediterranean descent. Since the pathogenesis of FMF is still unknown, and since physicians from the Mediterranean area have grouped numerous unrelated symptoms and signs under the disease, NIAMD grantees in Israel sought to determine whether or not the illness is a clear clinical entity.

From a long-term study of 262 FMF patients in Israel along with an additional 258 cases in the literature, the investigators were able to establish a definite diagnostic criterion: repeated, brief attacks of fever with abdominal, and often joint and chest pains of unknown cause. Amyloidosis, an often fatal state marked by formation of starchlike substances in various organs, sometimes accompanies the disease.

Israel's Jewish population is composed of different ethnic groups, each of which has its own history and geographical distribution and has been separated from the others for centuries. Of the Israel cases, 260 came from non-Ashkenazic groups, or those Jews of Sephardic (Spanish) and Iraqi descent. Six patients were Ashkenazic, or Jews of central and East European descent, and six were

Arabs. Within the group from the literature, 55 percent of the patients were Sephardic Jews, while the rest were gentile Armenians, Arabs, Italians, Spaniards, and Turks.

An investigation of familial incidence, consanguinity, and the family tree of 232 of the Israel cases indicated FMF is due to a complete autosomal recessive gene. This genetic analysis showed that FMF is frequent among the children of the same couple but rare in the couple itself, and that consanguineous marriage was much more common among the parents of patients with FMF than in the general population. The study also suggested that the amyloidosis of FMF is not a consequence of frequent attacks of fever but an independent genetically determined characteristic of the disease.

The researchers, E. Sohar, M. Pras, J. Heller, J. Gafni, and H. Heller, reporting in Revista Clinica Espanola, indicate that the characteristics of the disease place it as a nosological entity of rather frequent occurrence among Mediterranean ethnic groups. They also assume that its cause may be rooted in an inborn error of metabolism.

GASTROENTEROLOGY

A Greek physician 2,000 years ago once defined medicine as the study of the love affairs of the organs of the body. Certainly this definition fits well in the field of gastroenterology where a disease of one organ so often affects the well-being of another. Although gastroenterology is a relatively new area of interest to the Institute, huge numbers of persons who suffer from peptic ulcer, inflammatory enteritis, biliary colic, wasting cirrhosis, and other gastroenterological disorders have been helped by intramural and extramural research. The scope of such research now encompasses studies that utilize X-ray movies and other devices to learn what happens to food—in health and disease—from the moment it is swallowed until its products are completely metabolized. The past year's research includes the use of an experimental drug to provide dramatic relief for biliary cirrhosis patients, an especially significant accomplishment.

Dramatic relief provided for biliary cirrhosis patients

A drug capable of binding bile acids in the gut, thereby preventing their reabsorption, has been found to provide dramatic symptomatic relief for patients suffering from severe itching associated with biliary cirrhosis. The drug, used by NIAMD-supported researchers, was also effective in lowering serum cholesterol levels.

Pruritus, or itching, is usually a major complaint of patients with biliary cirrhosis, a rare disease resulting from interference with normal bile excretion. Until recently, the management of pruritus, thought to be due to bile acid deposition in the skin has been unsatisfactory. Itching can be so severe and unremitting that the patient may contemplate suicide.

From clinical studies supported by NIAMD and other sources, it was shown that the drug—MK–135 (Merck Sharp & Dohme), an anion exchange resin—acted as a potent bile acid sequestrant in four patients with severe pruritus associated with primary biliary cirrhosis. In two of the patients the pruritus and resulting insomnia were so incapacitating before treatment that they had seriously contemplated suicide and one had become temporarily psychotic.

The drug, administered in a 15-milligram daily dose for up to 2 months, dramatically relieved the patents' pruritus and insomnia within 2 weeks after treatment started, with an accompanying improvement in morale. Serum total bile acids which ranged from 10.4 to 14.2 milligram percent prior to treatment decreased in all subjects to levels ranging from 1.9 to 6.2 milligram percent. The NIAMD-supported investigators believe the resin acts by interrupting the cycle of bile acid secretion and reabsorption by the intestines through promotion of fecal excretion and possible mobilization of bile acid deposits from the skin.

The investigators found that a break in treatment was followed by a return of bile acid retention and pruritus in three of the patients. This was reversed upon reinstitution of therapy.

The drug was also found to cause a prompt and marked drop in serum cholesterol levels which was sustained as long as treatment continued. The scientists suggest that the resin apparently acts to increase cholesterol catabolish through its sequestering action.

On the basis of these studies, Drs. Theodore Van Itallie and Sami A. Hashim of St. Luke's Hospital and Columbia University, New York City, conclude that intestinal sequestration of bile acids can be effective in relieving pruritus and reducing serum levels of bile acids and cholesterol associated with biliary cirrhosis.

Excessive bacterial growth causes steatorrhea in post operative ulcer patients

NIAMD grantees have investigated the steatorrhea (fatty stools) that occurs in some ulcer patients who have had a large portion of their stomachs removed. The grantees have found that the fluid taken from intestinal loops bypassed by the operation contains high bacterial counts. This strongly indicates that excessive bacterial growth in these surgically created loops interferes with fat absorption.

Certain pathological processes result in formation of a blind loop of intestine which is thereby isolated from the flow of intestinal contents. Heavy bacterial growth occurs in such blind loops and, for unknown reasons, is frequently associated with steatorrhea. The defect in absorption of fats can be obviated by surgery or chemotherapy.

In a surgical procedure commonly employed in the management of patients with intractable ulcer, a blind intestinal loop is deliberately created. Frequently such patients present symptoms of severe steatorrhea and develop nutritional deficiency. NIAMD-supported grantees wondered whether these disabilities could be associated with the same factor, heavy bacterial growth, that is characteristic of the steatorrhea of spontaneously occurring blind loops.

The investigators found a mean of about 20,000 bacterial colonies per cubic centimeter in the duodenal fluid of the normal patients, as compared with about 600,000 in the postgastrectomy patients without steatorrhea, and between 200 million and 800 million in the steatorrheic patients. Antibiotic therapy given to two of the most severely afflicted patients was found to reverse the nutritional disorder to normal and to bring about a striking increase in body weight.

The grantees, Drs. F. Goldstein, W. Wirts, and S. Kramer, of Jefferson Medical College, Philadelphia, Pa., reported that clinical analysis revealed that postgastrectomy steatorrhea tends to occur in patients with long, poorly draining loops where diminished blood circulation encourages bacterial growth. Their report appeared in Gastroenterology.

Vitamin A deficiency produces liver lesions in germ-free rats

Germ-free rats on vitamin A deficient diets have been found by an NIAMD scientist to develop severe hepatic, renal, and adrenal lesions which were not present in conventional rats on the same diet. Since the liver in the conventional animal shows little or no morphologic changes in A deficiency, this study raises much speculation on the role of bacteria in vitamin A deficiency.

A prolonged lack of vitamin A causes, among other symptoms and signs, damaging alterations in the epithelia of various organs of the body which make the mucous membranes highly susceptible to bacterial invasion. In view of the constant occurrence of severe infection which obscures tissue changes, the Institute study with germ-free rats was undertaken to clarify the role of this infection and to provide a clear pathologic picture of changes which have heretofore been masked in studies of vitamin A deficiency.

Ten germ-free rats and a similar number of non-germ-free control animals were kept on a vitamin A-free regimen by Dr. David L. Beaver, of NIAMD's Laboratory of Pathology and Histochemistry (now at the School of Medicine, Washington University at St. Louis, Mo.) until 80 percent of the animals in each group had died. Three germ-free animals lived for 109 days while four controls survived 108 days, indicating that survival time is not increased in spite of the germ-free state.

The control animals exhibited the usual stigmata of A deficiency, including development of horny tissues (keratinizing metaplasia) and infection and inflammation of the tongue, salivary glands, respiratory and urinary tracts. The germ-free group showed similar effects which were modified by the absence of infection and inflammation, so that atrophy, degeneration, and necrosis became the predominant features of the disease in this group.

Lesions present in the germ-free group and not in the controls appeared in the adrenal glands and the kidneys. The most remarkable changes, however, occurred in livers where lesions varied from cytoplasmic droplets in occasional hepatic cells to actual liver necrosis. In several instances the necrosis alone was of sufficient magnitude to have been at least contributory to, if not the principal cause of, death. The focal necrosis and hyalinization of liver cells bore no resemblance to the diffuse cell death of "dietary liver necrosis" related to selenium deficiency.

Previous investigators have shown that the liver normally has a high concentration of vitamin A but exhibits no morphologic alteration in A deficiency. The hepatic lesions, unlike others produced in known deficiency states, raise questions as to why they should occur in germ-free animals and not in conventional ones. Dr. Beaver, reporting in the American Journal of Pathology, speculates that A deficiency without normal bacterial flora may cause a deficiency of another substance.

BASIC RESEARCH

Basic research is the lubricant for the wheels of clinical medicine. Although many medical advances have come from clinical research alone, many others have resulted from investigations not directly related to the understanding of disease processes. These other studies are concerned with the very fundamentals of plant and animal form and function, and make up the category known as basic research. The variety of studies done in this basic area is mirrored in such current findings, as the cracking of the genetic code—an accomplishment that provides new knowledge of the machinery of heredity, and the development of a technique to determine the weight of molecules.

RNA genetic code partially cracked

Institute scientists have succeeded in partially cracking the so-called genetic code which lies at the heart of the systematic reproduction of all living matter. This code, involving the two hereditary materials DNA and RNA (deoxyribonucleic acid and ribonucleic acid), provides the means for storing and transmitting genetic information; to understand it fully is one of the most important basic problems in biology.

DNA and RNA occur in all living cells and are now believed to direct the manufacture of proteins, life's most complex and important molecules. The core of the problem is how information is coded and carried from generation to generation in the structure of the DNA molecule, transmitted by "messenger" RNA and then used to direct the making of specific protein molecules from some 20 different amino acids.

In essence, what the NIAMD scientists, Drs. Marshall W. Nirenberg and J. Heinrich Matthaei, have done is to prepare a protein-synthesizing system from bacteria which can be "directed" with samples of synthetic RNA. They have observed that particular RNA samples of known structure direct the system to produce protein material incorporating only one of all the available amino acids. With one type of RNA only phenylalanine is incorporated; with another, only proline is incorporated. Since the structure or "code" of the RNA samples is known, it becomes possible to relate this structural code to the specific amino acid utilized.

The code contained in RNA can be thought of as a four-letter "language," each letter being represented by one of the four chemical bases that are attached to the long-chain RNA molecule. It is the particular sequence of these bases—adenine, guanine, cytosine, and uracil—that determines the code, and this sequence is believed to reflect the sequence of similar bases which occur in DNA. Since messenger RNA serves as a template against which 20 or more kinds of amino acids may be alined in the making of protein molecules, the problem of the code is to translate the 4-letter language of RNA into the 20-letter language of protein.

In the first part of their work the Institute scientists found that trace amounts of the DNA-destroying enzyme, DNAase, could inhibit amino acid incorporation into protein, suggesting that DNA functions all the way down to amino acid linkage. The work on the action of RNA was made possible in large part by their development of a cell-free protein-synthesizing system that remained stable. The one they used, derived from the micro-organism Escherichia coli, has hitherto been extremely unstable, but they found that the addition of the reducing agent, mercaptoethanol, could stabilize it remarkably. The system was provided with a full complement of amino acids and a source of chemical energy (adenosine triphosphate continuously regenerated by secondary reactions), and then various types of RNA were added.

The investigators found that the incorporation of individual amino acids into protein was dependent upon the addition of particular RNA templates. These could be either naturally occurring RNA or synthetic preparations of polyribonucleotides of known structure. When polyuridylic acid, a synthetic RNA containing only the base uracil was added, one and only one amino acid, phenylalanine, was incorporated. Similarly, when other synthetic RNA compounds were added containing specific bases specifically different amino acids were incorporated into the protein produced. Only "single stranded" RNA fibers were found to be active in the system. With this cell-free system it now seems likely that any type of protein can be made corresponding to a meaningful informational RNA.

These NIAMD findings provide information of considerable importance to biochemical research, and they represent the first experimental evidence which permits direct translation of the RNA code of protein synthesis. They are reported in the proceedings of the National Academy of Sciences.

First successful synthesis of pituitary hormone, ACTH, reported

The first successful synthesis of ACTH (adrenocorticotrophic hormone), the pituitary-produced hormone which stimulates cortisone production, has been achieved by University of Pittsburgh scientists supported in part by the National Institute of Arthritis and Metabolic Diseases. The researchers have announced at the university that the new synthetic hormone, having a molecular weight of 3,200, is the largest protein molecule ever reproduced synthetically and is 100-percent biologically active.

Production of the synthetic hormone culminates 17 years of research by other investigators and 7 years of study by the university group headed by Dr. Klaus H. Hofmann, chairman of the medical school's biochemistry department. The Hofmann team's first success was in the synthesis of a molecule comprised of the first 13 natural amino acid units in the ACTH chain. However, this and another 16-unit acid synthesied in early 1960 had only one one-thousandth of the adrenal-cortex-stimulating activity of natural ACTH.

Natural ACTH is produced by the pituitary gland and stimulates the cortex (outer part) of the adrenal gland to secrete cortisone and other hormones. Cortisone is used in the temporary remedial treatment of rheumatoid arthritis, rheumatic fever, and other diseases. Until now, only natural ACTH, produced by humans or animals, has been available for therapy or scientific research.

The Hofmann team constructed the synthetic hormone by putting together 23 natural amino acids. Employing many originally devised chemical procedures to achieve synthesis, the NIAMD-supported scientists assembled and purified the hormone, checked on the amino acid units' purity and arrangement, and checked the synthesized hormone for its biological activity. The new fully active synthetic verifies a hypothesis reported by Dr. Paul H. Bell of Lederle Laboratories in 1956 that the key to the biologic activity of natural ACTH resides within the first 24 amino acids of this 39-amino-acid molecule. Natural ACTH was first isolated from animal pituitary glands in 1943 by scientists at the University of California and at Yale University; the natural hormone's 39-amino-acid sequence was established in 1954.

The techniques developed for this synthesis, the University of Pittsburgh scientists believe, can now be used to create modifications of the natural ACTH molecule in hope of producing structually related compounds which possess specific desirable characteristics of ACTH and are free of other unwanted effects.

Although the full significance of the synthesis will only unfold in the future, "it is possible that it could help to clarify the functions of the pituitary gland; it will allow medical scientists to work with pure ACTH; and it could lead to an understanding of how the pituitary gland stimulates the adrenal gland's cortex to produce cortisone and other important steroid harmones," Dr. Hofmann reported. The tedious and involved chemical procedures, developed and used in the synthesis of ACTH by the Pittsburgh group, should pave the way for synthesizing even more complex protein and proteinlike molecules.

Metabolic adaptation occurs in mammals

An NIAMD scientist has shown that if the protein content of a rat's diet is increased from 15 to 60 percent, a fourfold increase occurs in the level of all the enzymes involved in the synthesis of urea. The study thus demonstrates an example of metabolic adaptation in mammals, an adaptive phenomenon previously known to occur in bacteria.

Metabolic adaptation is a well-established phenomenon in bacteria, yeasts, and certain other unicellular organisms. It occurs in response to changes in the type of substances used for energy requirements and in many cases is accomplished by an increase in the level of enzymes needed to break down the new compounds. Current work by Dr. Robert T. Schimke, of the Institute's Laboratory of Pharmacology and Toxicology, now shows that an adaptive phenomenon involving enzymes in the urea cycle occurs in mammals.

Although it has been known that increasing the protein content of the diet results in a higher rate of urea excretion, the mechanism by which this takes place has been unclear. Dr. Schimke's study was performed to clarify this mechanism and to determine whether the increased rate of urea synthesis, the final product of protein metabolism, was due to an increase in the levels of the five enzymes involved in urea synthesis, or possibly to other factors.

Rats were grown on diets containing various proportions of dietary protein and the livers of the animals were then analyzed to determine the levels of the five urea cycle enzymes: It was found that the levels increased about four times after the casein content of the diet had been increased from 15 to 60 percent. The enzyme levels rose within 48 hours after the change in dietary protein, and complete adaptation occurred within 8 days. During this period there was a corresponding increase in the amount of urea excreted in the urine.

Further studies by the NIAMD investigator showed that the increased urea production was not merely the result of supplying additional substrate for the enzymes to act upon, but was due to an actual increase in the amount of enzyme protein present. Also, when two of the enzymes, arginase and ornithine transcarbamylase were purified from livers of animals on both high- and low-protein diets, no qualitative differences were observed. This ruled out the possibility that the increased activity was due to some secondary effect, such as a hormonally induced redistribution of enzymic activity, or the release of activators or inhibitors.

Dr. Schimke's research supplies further evidence that in animals adaptive phenomena involving changes in the content of specific enzyme protein do exist, and as such can be considered analogous to adaptive phenomena found in bacteria.

Flourescent technique used to locate important enzyme

The Coons fluorescent antibody technique has been applied by scientists at NIAMD to localize an enzyme important to glycogen conversion. This work suggests that the technique may now be used to detect other enzymes which are undemonstrable by present procedures, and may aid research on diseases caused by enzyme defects.

The Coons technique involves an immunological binding of fluorescent-tagged antibody to antigen and serves as a precise method of detecting exogenous antigens— those injected or present as a result of infection. The Institute scientists have shown that this method can also be applied to study endogenous enzymes, that is, enzymes present in and native to the tissue.

In their work the investigators detected glyceraldehyde-3-prosphate dehydrogenase (GAPD), an enzyme important in glycolysis in the mitochondria of the wing and leg muscles of the roach. This insect was used because of the large size of its muscle fibers and a great concentration of GAPD in muscles of high-metabolic activity.

The antibody method for identifying an endogenous enzyme presupposes that the enzyme can be purified and can act as an antigen when injected into experimental animals. In this study, GAPD was isolated from rabbit muscle, purified, and injected into guinea pigs to obtain the antibody which is found in the gamma globulin fraction of the serum. Globulin with the antibody was then taken from the serum and coupled to a fluorescent dye.

When the roach muscle fibers were treated with the fluorescent antibody solution, the antigenic enzyme present in the fibers was bound by the fluorescent antibody. Difference of opinion has previously existed as to whether this enzyme is located in mitochondria or is dispersed within the sarcoplasm. The fluorescence appeared in a band of compact small mitochondria in a region referred to as the "I band." The gathering of the mitochondria in this area supports an earlier view that the I band is the seat of chemical energetic processes and glycogen conversion.

This study by Dr. E. W. Emmart and Dr. S. S. Spicer and W. A. Turner and J. G. Henson suggests further that the use of fluorescent antibody to localize enzymes within tissues may be applied to studies of specific enzyme defects in certain diseases.

Hypothesis on mechanisms of cell permeability provided

One-molecule-thick layers of fatlike molecules are providing the testing ground for new views on the permeability changes taking place in muscle and nerve cells. These NIAMD studies help explain the changes in movement of internal (potassium) and external (sodium) ions necessary to maintain life and function of the cell.

Dr. A. M. Shanes and his colleagues of NIAMD's Laboratory of Pharmacology and Toxicology have used the interactions of two opposing classes of drugs on an artificial "membrane" to study how the passage of ions in and out of nerve and muscle cells normally undergoes the changes responsible for the cells' bioelectrical behavior. The one-molecule-thick layers of lipoidal (fatlike) molecules used in these studies resemble natural membranes in their sensitivity and ability to exhibit well-known antagonisms to these drugs.

It has been shown that chemical agents such as local anesthetics, which belong to a class of compounds called stabilizers, affect permeability by adding their own bulk to the layer, thus increasing the packing of the molecules and therefore the pressure exerted by the molecules on each other. Dr. Shanes has confirmed this effect and further found that another group of agents, called labilizers (veratrine-related alkaloids), have the opposite effect; they reduce the pressure by removing molecules from the layer.

From this and other experimental evidence which he has produced, Dr. Shanes concludes that stabilizers interact with molecules surrounding sites of ion passage in living membranes, and by increasing the molecular pressure impede the passage of ions. Conversely, labilizers are able to reduce this pressure and facilitate ion movements.

Thus, these studies suggest that the permeability to ions—and hence the functioning of nerve and muscle—is dependent on the packing of membrane molecules, or on the related surface pressure. A more recent extension of these views by Dr. Shanes provides a new basis for understanding why changes in the bioelectrical potential across natural cell membranes (about 100,000 volts per centimeter) also cause permeability changes.

Dr. Shanes believes that these studies with monomolecular layers are essential as a basis for visualizing the complicated processes occurring in living membranes. Since permeability changes underlie all sensation, muscle and nerve action, and certain of the body's metabolic processes, knowledge of their mechanism may help explain such diseases as myotonia, myasthenia gravis, and diabetes.

Pituitary hormone may have new role in thyroid function

Studies by NIAMD scientists on the pituitary gland's thyroid stimulating hormone (TSH) suggest that its primary function in the regulation of the thyroid is the stimulation of glucose oxidation in the gland. As a result of this, the thyroid can secrete its own hormone, thyroxin, which is necessary to the regulation of the body's metabolism.

Drs. Ira Pastan and James B. Field of NIAMD's Clinical Endocrinology Branch have shown that small amounts of TSH rapidly stimulate the thyroid's ability to oxidize glucose sugar. This effect was seen within 5 minutes after the addition of TSH to a medium containing thyroid slices. The fact that TSH, a product of the pituitary's anterior lobe, was effective in such small amounts and so rapidly stimulated glucose oxidation, suggests that this is its primary action on the thyroid and that previously reported thyroidal effects of TSH, such as in iodine and phospholipid metabolism, are secondary.

TSH stimulation of glucose oxidation was specific or peculiar to the thyroid since TSH had no effect on oxidation of glucose by other organ tissue slices, and none of the other anterior pituitary hormones affected the thyroid. It was also shown that the level of TSH present in human blood (a microscopic amount) was effective in stimulating oxidation.

Although the thyroid's ability to absorb glucose from the medium (glucose uptake) was also stimulated by TSH, this did not seem to be the primary mechanism of the increased glucose oxidation. This conclusion was reached since insulin, which is thought to act on or to aid the transport of glucose through cell walls, also stimulated glucose uptake but not the oxidation of glucose to carbon dioxide.

In the study it was subsequently shown that the increase in glucose oxidation was due to a rise in the concentration of a vital cofactor of glucose oxidation, triphosphopyridine nucleotide.

Acetylcholine, a substance released from nerve endings during transmission of nerve impulses to muscles and other structures, also increased glucose oxidation and uptake by the thyroid. However, TSH did not appear to act by stimulating acetylocholine release, since atropine was able to inhibit the increase caused by acetylcholine but not that produced by TSH. Epinephrine, norepinephrine, and serotonin, substances known to stimulate body organs and to affect the thyroid's metabolism of iodine, also were found to stimulate glucose oxidation.

This new finding on TSH action, reported by Drs. Pastan and Field, represents a new approach to thyroid research and leads to a better understanding of how hormones control body functions.

Source of blood platelets reported

The application of fluorescent antibody technics to the study of human blood platelets has provided more evidence that the platelets arise from megakaryocytes in bone marrow. The studies have diagnostic importance in cases of idiopathic thrombocytopenic purpura. They were reported by grantees of NIAMD working with grantees of the National Heart Institute at the University of Pittsburgh School of Medicine.

Many investigators now accept the hypothesis that the platelets arise from megakaryocytes, giant cells in the bone marrow. More evidence to support this belief has recently been reported by investigators at the University of Pittsburgh School of Medicine. By using relatively new fluorescent antibody technics, these scientists have demonstrated a common antigenic makeup in platelets and megakaryocytes.

The studies involved the use of an antiplatelet serum which had been tagged with fluorescein and then used as a stain for platelets and mekagaryocytes. It was found that both types of cells showed a specific bright green fluorescence, indicating a similar antigenic structure. When megakaryocytes present in normal bone marrow smears were stained, formed platelets with specific fluorescence could be seen in the periphery of the large cells, as well as budding from them. Rare nonplatelet forming megakaryocytes fluoresced also, but their fluorescence was distinctly different, with a diffuse homogenous character.

The grantees then used the technique to study material taken from patients with idiopathic thrombocytopenic purpura (ITP) a blood disorder of unknown cause which is associated with a pronounced reduction of platelets. One of their findings was that the megakaryocytes from bone barrow of ITP patients could be easily distinguished from most normal megakaryocytes, the "ITP megakaryocytes" having an homogenous fluorescence and showing little or no sign of platelet production. This difference may have diagnostic value in suspected cases of ITP. Further studies, done on spleen sections, revealed that there was a marked increase in the number of platelets present—possibly sequestered—in the spleen of ITP patients. (The sections were taken at autopsy.)

These investigations demonstrate that the fluorescent antibody technic is a valuable tool for studying platelets and megakaryocytes, and one which may provide needed information about the structure and localization of these cells. A report of the work by Drs. Jacinto J. Vasquez and Jessica H. Lewis appeared in Blood.

Blood found to be important site for conversion of steroid hormones

NIAMD grantees have found that blood of various mammalian species can alter steroid hormones in a surprisingly short time—as little as 10 minutes incubation time. Chromatographic analysis showed that each of the hormones tested undergoes alterations in chemical structure, the trend being towards the formation of biologically inactive forms. Blood may thus play an important role in steroid metabolism.

NIAMD-supported studies at the Southwest Foundation for Research and Education, San Antonio, Tex., are a continuation of earlier investigations which showed that the steroid hormone estrone undergoes conversion when incubated in blood alone. This observation led to the present work to see if other steroids are similarly affected and if this is a species-specific or a general phenomenon. Hydrocortisone, testosterone, and estrone were used, and incubated in blood from various species, including the human, for periods ranging from 10 minutes to 48 hours. The blood mixtures were then chromatographed on paper to determine the presence of various steroid metabolites and conversion products.

The Institute grantees found that all the steroids underwent some alteration in each type of blood tested: mouse, guinea pig, steer, cow, baboon, and human. In addition, the chromatographic and spot test data showed that the specific conversion products as well as the relative amounts formed were species-characteristic; there was even a difference in the manner in which steer blood metabolized hydrocortisone as compared to cow blood.

Clearly, a complete description of the conversion products will eventually be required, the investigators reported, but certain generalities can be drawn from the present data. The reaction is rapid and probably enzymatic, with significant quantities of the hormones being converted in as little as 10 minutes. The trend in these metabolisms is for the hormones to be converted to biologically less active forms (hydrocortisone to the "tetrahydro" forms, testosterone to a more oxygenated structure, and estrone to estradiol 17a).

Although the liver has the capacity to convert steroids in large quantity and with great rapidity, only a fraction of the circulating blood from the heart passes through the liver at each pass; also, the immediate secretions of the endocrine organs do not enter the portal (liver) circulation. Thus, when considering the blood as a steroid-metabolic "organ," these current studies suggest that the steroid conversions occurring in the blood may be of equal if not greater significance to homeostasis than those which occur in other organs. The research was reported by Drs. Leonard Axelrod and Nicholas T. Werthessen in the journal Endocrinology.

Spermine helps stabilize the DNA molecule

Dr. Herbert Tabor of NIAMD has demonstrated that the "transforming ability" of DNA is markedly stabilized by spermine, a polyamine found widely distributed in animal tissue and fluids. His study shows that spermine protects the genetically important DNA molecule from being denatured by heat, and further indicates the great importance of DNA's molecular configuration to its function.

Spermine and other related polyamines are organic compounds formed from ammonia, and although they are not uncommon their function remains largely unknown. Dr. Tabor and other investigators in NIAMD's Laboratory of Pharmacology and Toxicology have previously found that these polyamines have a stabilizing effect on vital cell components such as mitochrondia, the organelles in and around which many of the cell's chemical reactions take place, and such bacterial materials as protoplasts and viruses (bacteriophage).

Dr. Tabor has now extended this work to DNA, particularly to DNA's ability to transform one type of organism into another, and how spermine may protect that ability from inactivation by heat. He used a transforming DNA isolated from a strain of Bacillus subtilis, an organism that does not require the amino acid tryptophan. When active, this DNA is able to transform tryptophan-dependent organisms into tryptophan independent ones.

The scientist found that if the transforming DNA alone was heated to 70° (its "melting out" temperature), it lost half its transforming activity. However, if spermine was present, a much higher degree of heating—92°—was required to produce a comparable degree of inactivation.

The mechanism of this protective action of spermine against heat-denaturation of DNA is not known. Most likely spermine tends to strengthen the intramolecular bonds of DNA by forming a complex with the phosphate groups that dot the surface of DNA's spiral-like molecule. Further studies may lead to a better understanding of some of the normal tissue constituents that determine the functional configuration of DNA molecules, and thus their biological activity.

Technique developed to determine molecular weight

A simple method for determining the molecular weight of large molecules such as enzymes has been developed by NIAMD scientists. The new method does not require the complex "analytical" ultracentrifuge and can be used to determine the molecular weight of individual enzymes in a protein mixture.

Calculation of the molecular weight of large molecules is usually based on data obtained from studies of the molecule in an "analytical" ultracentrifuge. This apparatus is complex and expensive, and necessitates the use of pure substances only. Recently, Drs. Robert Martin and Bruce N. Ames, of the Institute's Laboratory of Biochemistry and Metabolism, have developed a method which utilizes the smaller, relatively inexpensive, "preparative" ultracentrifuge and one which is applicable to any kind of enzymes in protein mixtures. The technic is a modification of one previously used for viruses and subcellular particles.

Using their technic, the scientists fill a centrifuge tube with a solution of sucrose and then "layer" the mixture protein solution on top of this sucrose gradient. During centrifugation each enzyme present in the layer moves at a characteristic rate through the gradient depending upon its molecular weight, and when the apparatus is stopped the enzymes are separated into zones at different levels in the gradient. A hole is then punched in the bottom of the centrifuge tube and the solution is fractionated by collecting drops.

These fractions permit analysis for any of a variety of properties, including enzymatic activity, radioactivity, or chemical properties. Thus, a particular biological material in a crude multicomponent mixture may be localized by one of its physical properties.

The accuracy of the simple ultracentrifugation method is within 5 percent of the standard analytical techniques and has the advantage of utilizing much smaller volumes of material and may be used for enzyme purification. In addition, if may be a valuable research tool for studying the properties of enzymes, and is now being used in an attempt to establish whether there is a correlation between the size of a gene and the size of a protein synthesized by the gene. Details of the new analytical techniques were reported in the Journal of Biological Chemistry.

Unusual activity of vitamin C demonstrated in protein metabolism

Exploration of some of the many biochemical ways in which vitamins can act has disclosed an unusual role for vitamin C (ascorbic acid) under certain experimental conditions. NIAMD Drs. Bert N. LaDu and Vincent Zannoni have shown that vitamin C acts to "protect" one of the enzymes needed in the metabolic degration of tyrosine in the body. While this protective role is necessary for normal metabolism, it is a much less specific function for vitamin C than had been supposed, and provides an interesting example of the multiple functions the vitamin may have.

Vitamin C has been known to have an important role in maintaining normal tyrosine metabolism, a process which takes place in a series of reactions. Before they will take place, however, several enzymes must be present to promote the reactions and control their speed, and at one time it was thought that vitamin C formed part of one of the enzymes, p-hydroxyphenylpyruvic acid oxidase or PPAO. This enzyme facilitates the second step in tyrosine metabolism, the conversion of p-hydroxyphenylpyruvic acid to homogentisic acid. Such an action by vitamin C would be similar to that of some of the B vitamins which participate in other metabolic processes as indispensable components of the enzymes involved.

The Institute scientists have now found that instead of becoming an intrinsic part of PPAO, vitamin C protects this enzyme from being inhibited in the presence of excessive amounts of p-hydroxyphenylpyruvic acid. They were able to demonstrate this protective effect in guinea pigs that were deficient in vitamin C and had been fed extra amounts of tyrosine in their diet. The extra tyrosine caused large amounts of p-hydroxyphenylpyruvic acid to accumulate in the liver and within 2 hours 80 percent of the PPAO present in the liver had been inactivated. On the other hand, animals that were given vitamin C showed no reduction in PPAO activity after tyrosine loading, indicating that the vitamin prevented inactivation. The exact mechanism of this inactivation and protection is still being investigated.

Other compounds chemically unrelated to vitamin C, including the blue dye 2,6-dichlorophenolindophenol, were also able to prevent inhibition of the enzyme in ascorbic acid deficient guinea pigs given large amounts of tyrosine. However, these compounds did not prevent guinea pigs from developing weight loss, hemorrhages, and other signs of scurvy (vitamin C deficiency).

"Perhaps future experiments will reveal instances in which ascorbic acid acts as a 'conventional' vitamin in some of the other biochemical processes which are deranged in scurvy. The elucidation of its role in tyrosine metabolism illustrates one of the variety of ways in which this essential carbohydrate participates in biochemical and physiological reactions," the NIAMD investigators concluded.

Growth hormone found to act directly on amino acid transport

NIAMD grantees working with grantees of the National Cancer Institute have found that bovine growth hormone administered to rats stimulates the transport of amino acids into the cell. Their study indicates that this is a direct action of growth hormone and further clarifies the mechanism by which the hormone accelerates protein synthesis.

Use of a nonmetabolized amino acid has enabled the grantees to pinpoint one important site of action of growth hormone. Their studies indicate that growth hormone rapidly stimulates the transport of amino acids into the cell, thereby permitting the protein synthesis essential to growth.

The growth hormone of the pituitary has long been known to decrease plasma-free amino acid levels: this has been thought to occur by increased uptake of amino acids by cells. This increased uptake could either by one of the causes of increased protein synthesis or the increased uptake could be the result of a primary increase in protein synthesis within the cells which would deplete cell amino acids and indirectly accelerate the entrance of more amino acids. The present work indicates that the growth hormone directly affects amino acid transport into the cells.

The grantees studied the transport step by using alpha-amino-isobutyric acid (AIB), an amino acid which is not metabolized by the cell but which is transported in a manner similar to naturally occurring amino acids. AIB was radioactively tagged and injected into hypophysectomized rats. Changes in tissue distribution of AIB after bovine growth hormone administration were then measured and taken to mean a change in amino acid transport into cells. The more sensitive hypophysectomized rats were used after earlier studies by the same investigators had shown that growth hormone increased amino acid uptake in normal rats.

Growth hormone was found to act extremely rapidly in increasing the AIB disappearance rate from the rat serum. This was accompanied by increased amounts of amino acid particularly in skeletal muscle, but also in kidney, heart, and liver.

Use of the nonmetabolizable AIB by Drs. T. R. Riggs and L. M. Walker of the University of Michigan has made it possible to determine that at least one site of action of growth hormone is the essential first step in protein synthesis, transport of free amino acids into cells.

PROGRAM DEVELOPMENTS

"Report to the Nation" cites progress in arthritis and metabolic diseases

The National Institute of Arthritis and Metabolic Diseases celebrated its 10th anniversary with a special "Report to the Nation" on March 9 in the clinical center auditorium. Presented at the request of Senator Lister Hill and Congressman John E. Fogarty to inform the public about research progress during the Institute's first decade, the report was opened by Dr. Floyd S. Daft, NIAMD's Director. Appearing on the program were Health, Education, and Welfare Secretary Abraham Ribicoff, Surgeon General Luther L. Terry, Dr. Ronald W. Lamont-Havers, Medical Director of the Arthritis and Rheumatism Foundation, and Senator Hill. Scientific speakers included Drs. Currier McEwen, George W. Thorn, Franz J. Ingelfinger, DeWitt Stetten, Jr., and Arthur Kornberg.

One of the discoveries of great importance in arthritis has been the rheumatoid factor in patients with rheumatoid arthritis, Dr. McEwen said, and the subsequent finding that this material belongs to the gamma globulin fraction of the serum, thus suggesting its antibody nature. Further studies showed that the factor was probably a byproduct of rheumatoid arthritis, and that its presence in asymptomatic blood relatives of patients suggests that heredity is involved in this disease. In clinical studies, the use of a newly developed program of cooperative testing of new drugs may provide adequate and rapid appraisals of medications.

Dr. Thorn praised NIAMD-supported studies in detecting early diabetes or diabetes predisposition which, he said, will make possible large-scale efforts in this area. Clinical advances are also expected from developments which permit accurate measurement of insulin in the blood, and from studies of the hormone's exact chemical nature. The possible use of synthetic insulin or human insulin is under study in view of the complications which develop with presently used animal insulin preparations. There are many indications that a study of diabetes—with its rapid rate of progressive and serious vascular changes—offers a unique opportunity to make critical observations on the fundamental nature of changes which predispose to early vascular disease in general.

Speaking about gastroenterologic research, Dr. Inglefinger said Institute grantees are now using specially developed X-ray movies and pressure-recording devices to elucidate the precise mechanical steps by which food passes through the esophagus, is milled in the stomach and transported down the intestines. New laboratory techniques are being used to demonstrate how gastric and pancreatic enzymes act and how digested foods pass from the intestinal lumen into the body fluids. Developments which permit the application of fiber optics to the examination of viscera may soon bring tubing devices as flexible as spaghetti to examine all parts of the alimentary canal.

Basic research by NIAMD scientists had shown that children afflicted with galactosemia lacked a single enzyme necessary to convert galactose into glucose, Dr. Stetten reviewed. This study has led to a specific diagnostic test to permit early diagnosis of this rare disease, and further investigation to gather evidence of its genetic character which points to a Mendelian recessive transmission. Present investigations hint at the possibility of circumventing the biochemical defect. Other metabolic diseases may also be explained in terms of specific enzyme defects.

One of the major advances in the past decade was the recognition of deoxyribonucleic acid (DNA) as the genetic substance in all living cells. Dr. Kornberg said this "book of life, or code" contains instructions for building the intricate structure and enzymatic machinery of the cell. Another function of this complex chemical fabric is its overall provision for the preservation of the race. Institute scientists and grantees are beginning to develop greater understanding of nucleic acids through investigation of their chemistry and enzymology. These advances and other progress in technology will help decipher the DNA code, which, in turn, will sharply define and perhaps solve some problems involving growth, cancer, and aging.

A special plaque honoring Dr. Daft, Director of NIAMD, for his continuing contribution to the support of arthritis research and training was presented at a dinner held following the Institute's "Report to the Nation." Among the invited guests were National Advisory Council members, members of professional societies, representatives from voluntary health agencies, and staff members of PHS and NIH.

The plaque was presented jointly by the American Rheumatism Association and the Arthritis and Rheumatism Foundation to Dr. Daft "in recognition of his constant devotion to and effective support of a national program of research, training, and education in arthritis and connective tissue diseases."

MONDAY, FEBRUARY 19, 1962.

ALLERGY AND INFECTIOUS DISEASE ACTIVITIES

WITNESSES

DR. JUSTIN M. ANDREWS, DIRECTOR, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

RICHARD L. SEGGEL, EXECUTIVE OFFICER, NATIONAL INSTITUTES OF HEALTH

JAMES F. KELLY, DEPARTMENT BUDGET OFFICER

Object classification

[In thousands of dollars]

	1961 actual	1962 estimate	1963 estimate
11 Personnel compensation:			
Permanent positions	3,416	3,948	4,166
Positions other than permanent	66	68	68
Other personnel compensation	118	123	123
Total personnel compensation	3,600	4,139	4,357
12 Personnel benefits	413	433	445
21 Travel and transportation of persons	161	207	252
22 Transportation of things	50	75	80
23 Rent, communications, and utilities	83	97	97
24 Printing and reproduction	9	10	10
25 Other services	474	3,249	4,506
Payment to the "National Institutes of Health management fund"	2,876	3,788	4,079
26 Supplies and materials	733	963	1,026
31 Equipment	332	494	395
41 Grants, subsidies, and contributions	34,056	41,657	44,105
Subtotal	42,787	55,112	59,352
Deduct quarters and subsistence charges	9	10	10
Total obligations	42,778	55,102	59,342

Personnel summary

	1961 actual	1962 estimate	1963 estimate
Total number of permanent positions	593	656	691
Full-time equivalent of other positions	10	11	11
Average number of all employees	571	627	662
Number of employees at end of year	603	641	681
Average GS grade	6.4	6.9	6.9
Average GS salary	$5,897	$6,103	$6,091
Average salary of ungraded positions	$4,448	$4,500	$4,500

Program and financing

[In thousands of dollars]

	1961 actual	1962 estimate	1963 estimate
Program by activities:			
1. Grants and related contracts:			
(*a*) Research	28,081	34,697	37,145
(*b*) Fellowships	1,199	1,610	1,610
(*c*) Training	4,776	5,350	5,350
Total, grants and related contracts	34,056	41,657	44,105
2. Direct operations:			
(*a*) Research	8,358	9,592	10,005
(*b*) Collaborative studies		2,050	4,050
(*c*) Review and approval of grants	519	786	894
(*d*) Administration	211	244	288
(*e*) Rocky Mountain Laboratory facility		750	
Total, direct operations	9,088	13,422	15,237
Total program costs [1]	43,144	55,079	59,342
Change in selected resources [2]	−366	23	
Total obligations	42,778	55,102	59,342
Financing:			
Comparative transfers to other accounts	1,002		
Unobligated balance lapsing	220	972	
New obligational authority	44,000	56,074	59,342
New obligational authority:			
Appropriation	44,000	56,091	59,342
Transferred to "Operating expenses, Public Buildings Service," General Services Administration (75 Stat. 353)		−17	
Appropriation (adjusted)	44,000	56,074	59,342

[1] Includes capital outlay as follows: 1961, $243 thousand; 1962, $588 thousand; 1963, $395 thousand.

[2] Selected resources as of June 30 are as follows: Unpaid undelivered orders 1960, $586 thousand. (1961 adjustment $77 thousand); 1961, $297 thousand; 1962, $320 thousand; 1963, $320 thousand.

Mr. Fogarty. The committee will come to order.

We have before us this afternoon Dr. Andrews, with the request for Allergy and Infectious Diseases.

GENERAL STATEMENT

Dr. Andrews, do you have a statement for the committee?

Dr. Andrews. Yes, sir. May I file this and discuss some of the points in it?

Mr. Fogarty. All right.

(The statement referred to follows:)

STATEMENT BY DIRECTOR OF NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, PUBLIC HEALTH SERVICE

Mr. Chairman and members of the committee, 75 years ago, in 1887, the first bacteriological laboratory in the present Public Health Service was established in a single attic room at the Staten Island Marine Hospital, a forerunner of the USPHS Hospital. This early "Laboratory of Hygiene" was in fact the nucleus of the present National Institutes of Health, and particularly the progenitor of today's National Institute of Allergy and Infectious Diseases.

Dr. Joseph J. Kinyoun, who set up the laboratory and was the first director of the National Institutes of Health, stated that "the scope of work of this character is constantly widening, its utility unquestionable."

Fundamental studies of virus-cell relationships, of virus inhibitors such as interferon, of parasite-host factors, or of the obscure but significant interaction between fungi and bacteria competing for life in a test tube as they may in man—even basic studies such as these will eventually prove utilitarian in the saving of lives, the sparing of suffering, the improvement of our health and economy.

The work of the National Institute of Allergy and Infectious Diseases is also pertinent to cancer, rheumatic heart disease, arthritis, biological warfare defense, and other major problems. We have cooperative projects with other Institutes to study conditions such as cystic fibrosis, neurologic diseases of childhood, the effects of maternal virus infections on the unborn child.

Our view of microbiological research today takes in both world health problems and diseases of special importance to the United States. The Institute is cognizant, for example, of the rising incidence of infectious hepatitis in our Nation. Together with the Communicable Disease Center and the environmental health facilities we share in efforts to prevent or control this disease. One of the larger new grants approved after the November meeting of the National Advisory Allergy and Infectious Diseases Council was for studies of infectious hepatitis to be undertaken at the State University of Iowa.

We plan fully to exploit our special facilities for research on internationally important diseases such as schistosmasis, malaria, and filariasis. The International Centers for Medical Research and Training and other resources should prove useful in expanding these investigations.

Antibiotic resistant staphylococci, antimalarial-drug resistant Plasmodidae, insecticide resistant mosquitoes merely exemplify the propensity of pathogenic agents and vectors to evade attack. The pace of the attack today, however, will undoubtedly extend our control.

This Institute is establishing major collaborative projects to produce standard virus reference reagents to aid a number of fields of research. A specific vaccine development program is being set up. This will be augmented by extensive field trials.

VIRUS DISEASES AND VACCINE DEVELOPMENT

No other disease agents are implicated in as wide a range of illness as viruses. Not only are they responsible for a long list of known diseases ranging from the common cold to yellow fever, but their relationship to chronic illness, including heart disease, cancer and neurologic diseases is increasingly suspect. In respiratory disease studies alone, the number of known viruses has increased from 2 to 98 serologic types in less than a decade.

One segment of the viral disease problem—respiratory tract illness—accounts for more disability over the lifespan of the average American than all other acute illnesses combined. The amount of time lost from productive pursuits represented by four to six respiratory episodes per adult per year—the major cause of work absenteeism in this country—is only a partial measure of the pervasiveness of this syndrome in our culture. Even in terms of mortality, respiratory disease far exceeds poliomyelitis and other illnesses which have attracted extensive attention and financial support. Each year 50,000 to 60,000 deaths are attributed to pneumonia and other forms of acute respiratory disease, a good proportion of which are caused by viruses.

Not only is respiratory disease a massive problem in adults, but children are particularly susceptible because of their immunologic inexperience. Over more than 5 years, Institute scientists have been studying such illnesses in a closely defined population of young children in the District of Columbia. A wealth of information has been collected about specific viruses implicated in a large percentage of their illnesses. Nearly 60 immunologically different serologic types of viruses have been isolated, many of them previously unrecognized or unclassified.

In 1961 Institute scientists assessed the role of one of the viruses, called the respiratory syncytial virus, in an extensive outbreak of pneumonia in the children under long-term study. Although the association of respiratory syncytial virus with human disease had already been reported in earlier studies by Institute investigators and their collaborators in other institutions, this was the first time it had been found to be responsible for serious illness, affecting 36 to 90 children in 1 study population.

It is now possible to identify viruses or other filterable microbes as the causative agent in 60 percent of children hospitalized for severe respiratory illnesses. These include influenza virus (5 percent), parainfluenza virus (15 percent), Eaton agent (10 percent), respiratory syncytial virus (20 percent), and adenovirus (10 percent). As recently as the early 1930's, only the influenza viruses were known to cause human respiratory disease. Today we know that at least 20 viruses cause recognizable human disease. These are among the approximately 100 new serologic types of viruses identified in the laboratory since 1953.

Many virologists believe that the development of preventive vaccines offers the most practical prospect for eventual control of the acute respiratory diseases, and that respiratory illnesses no longer have to be accepted fatalistically as an inevitable corollary of modern life. The current pace of research calls for an equal effort to develop and evaluate immunizing vaccines useful to the practicing physician.

It is true that a vaccine far beyond the complexity of current virus vaccines will be needed to control the multiplicity of acute respiratory disease. Present vaccines with which there has been extensive experience—such as those for poliomyelitis, influenza, and measles—are relatively simple when contrasted to one which must be designed to attack the numerous viruses of upper respiratory disease. For polio vaccine alone, years of basic and developmental work and an estimated $50 million were invested in the first successful product—a vaccine effective against only three virus strains.

In spite of the recognized complexities of the research problem, virologists believe that an attack can be launched with the weapons already in their possession. A vaccine development program, with well-defined goals, is a promising step in the direction of practical application of existing virologic information, and may also provide a stimulus for additional basic laboratory studies.

It is apparent that practical steps must be taken toward the development of vaccines and the improvement of those already available. The Institute has assumed responsibility for a program designed to develop and test prototype vaccines. This program is a logical extension of basic virologic investigation. The direction of the program, centered in the Institute, will rest with a Board for Vaccine Development whose members will be chosen from university and government research groups actively working with respiratory viruses.

While a major emphasis is placed on respiratory tract viruses, the Institute also conducts research on rabies, yellow fever, Colorado tick fever, and other virus diseases. To evaluate and put in perspective the work reported last year on the first experimental vaccine against measles, an International Conference on Measles Immunization was held at the National Institutes of Health. Cosponsored by this Institute, the Division of Biologics Standards of NIH, and the University of Colorado, and Conference brought together approximately 300 virologists from 20 countries. European, African, Asian, South American, Australian and Middle Eastern scientists, as well as those from North America, presented their data. They covered the worldwide epidemiological aspects of measles, properties of attenuated measles virus strains, field data on the use of live attenuated vaccines, problems of production and biologic control, and predictions about the future of measles immunization. A safe and effective vaccine against this disease which afflicts 70 to 95 percent of our children will be a boon to national health comparable in importance to poliovaccines. Although the disease itself may be mild, complications can be serious. They include pneumonia and brain damage, as well as impairment of hearing and sight.

Other viruses isolated in the past year by Institute scientists include 4 additional adenoviruses, bringing to 28 the number of human adenovirus types now recognized. Two new animal viruses described are the HADEN (hemadsorbing, enteric) virus of cattle and a virus from mice, tentatively named mouse thymic virus.

Coxsackie viruses are enteroviruses which cause a variety of mild to serious diseases. In one study, an Institute grantee in California has documented the association of this virus with illness that simulates poliomyelitis. The investigators believe that an increasing proportion of cases of infectious paralytic disease coming to medical attention will be these nonpoliomyelitic illnesses.

VIRAL REFERENCE REAGENT PROGRAM

One of the urgent needs in virology is standardized virus reagents which will assist research workers to identify the viruses they isolate. To this end, a coordinated program is being developed to provide reagents which can be made available eventually to virologists all over the world.

Two related but distinct needs must be met through this coordinated program. It must provide reference reagents which investigators may use as reliable standards of comparison to assure uniformity of identification of viruses as they are discovered. It must provide a means of furnishing diagnostic reagents which can be used to screen viruses being studied in epidemiologic and other research by grantees and other qualified investigators.

The virus reagent program is being designed to meet the extramural and intramural needs of all Institutes at the National Institutes of Health in their programs for virus research.

Specific antisera and prototype viral antigens for the 37 known adenovirus types are already being produced, standardized, packaged and certified. These will become available over a 2-year period and the first of them is expected early in 1962.

In addition to the adenoviruses, the expanded program will include other respiratory and related viruses, enteric viruses, arthropod-borne viruses, and miscellaneous viruses. The program will be guided by a Board for Virus References Reagents comprised of consultants outside the government, plus staff representatives of interested Institutes within the National Institutes of Health. This Board will utilize the advise of several expert technical panels of nongovernmental consultants.

The new program, recognizing the need for coordination of both production and distribution of virus reagents, should insure that all groups of viruses will be covered with minimum duplication of effort. Its broad objective—improvement of research in virology—can contribute concretely to many virus research areas—vaccines, viral diseases of all kinds, virus-cancer relationships and basic biomedical studies using viruses as models.

EATON AGENT, A PLEUROPNEUMONIALIKE ORGANISM (PPLO)

"Eaton agent," recently shown to be an important cause of pneumonia, has been grown for the first time in a cell-free medium, in a collaborative project with the Wistar Institute in Philadelphia, and revealed as a member of an obscure group of subbacterial microbes called "PPLO" (pleuropneumonialike organisms). This is the first PPLO linked with human disease although these organisms have been known to cause respiratory disease in cattle. The Eaton agent, tentatively classified as a virus since its discovery by Dr. M. D. Eaton in 1944, is estimated to cause from 10 to 50 percent of atypical pneumonia.

In confirming their findings, researchers of the National Institute of Allergy and Infectious Diseases, the Wistar Institute of Anatomy and Biology and the National Institutes of Health Division of Biologics Standards used immunofluorescent tests, microscopic examinations and other tests, and made comparisons with known PPLO.

Their studies explain why tetracycline, an antibiotic ineffective against viral illness, was curative in cases of Eaton agent pneumonias.

Growth of Eaton agent on artificial media may aid in rapid diagnosis of infection and provide a stimulus to the preparation of vaccine.

The association of one variety of PPLO with human respiratory disease suggests that PPLO other than Eaton agent may be capable of producing respiratory disease in man. The possibility of PPLO infection should be considered in any systematic investigation of the presently unexplained segment of human respiratory disease.

ALLERGY-IMMUNOLOGY

Knowledge and training in immunology are required to meet a vast array of disease problems. The skills of the immunologist are necessary to carry forward vaccine development programs and basic cancer studies; they are needed for the understanding of grotesque pathology as well as of the more common allergies such as hay fever and asthma. For example, the grotesque disfigurement of elephantiasis—a complication of the parasitic disease, filariasis—is due to lymphatic obstruction which is believed to be caused or augmented by allergic sensitivity to proteins of the invading parasite.

There is an acute shortage of trained immunologists to meet these problems. We are encouraged, however, by the high percentage of young physician candidates for training at our Institute who seek out our Laboratory of Immunology. This laboratory, founded only 4 years ago, receives almost weekly requests from young physicians for training. The majority of these candidates undoubtedly foresee the importance of immunology and its newer techniques to the various fields of medicine.

In addition to training at Bethesda, the Institute supports 37 immunology training grants in the amount of about $1,250,000.

There are about 200 active research grants in the amount of over $4 million, largely for studies in allergy-immunology. For example, at Johns Hopkins Institute grantees have been making a 5-year comparison of the therapeutic as well as the growth-inhibiting effects of a variety of adrenal cortical hormones in prolonged treatment of children with intractable perennial bronchial asthma. During the past year, grant-support and Institute immunologists continued to extend the usefulness of the fluorescent antibody technique—as an aid for disease diagnosis as well as for basic laboratory studies. For example, no reliable serological test has been available in the past to follow the course of antibody production in malaria infections. Preliminary results from an Institute study suggest that the fluorescent antibody technique provides a sensitive means for doing so, a procedure which should lead to the accumulation of new information. Such a specific method could prove useful in the worldwide eradication of malaria.

There are areas of disease which can be further clarified only by research founded on basic immunology. These are the "autoimmune" diseases, or, more properly, diseases of uncertain causation believed to occur when an individual becomes allergic or sensitive to substances present within his own body. Stated another way, these diseases appear to be caused by immunologic anatagonisms between altered tissues or tissue products of the individual and his own defense mechanisms, which no longer recognize these tissues as belonging to the individual.

Under investigation in our Laboratory of Immunology are such diseases as lupus erythematosus, nephritis, rheumatoid arthritis, and others in which autoimmune bases are known or suspected.

Allergic thyroiditis has been produced experimentally in a strain of inbred guinea pigs by Institute scientists, providing a model for study of one form of human thyroid disease known as Hashimoto's thyroiditis, where inflammation of the thyroid is found and where evidence points to its being an autoimmune disease. The scientists produced a similar inflammation of the thyroid by injecting strain 13 inbred guinea pigs with extracts of thyroid glands of other guinea pigs of the same strain. Such a procedure is comparable to injecting the animals with their own thyroid tissue because the strain 13 pigs are so immunologically similar they accept skin grafting from one another as if they were identical twins. The scientists therefore were able to exclude the possibility that the inflammation was due to natural defense reactions to foreign tissue which would occur in other animals.

These "histocompatible" animals have been a valuable research tool in our investigations. Now lymph nodes and other tissues as well as thyroid and skin may be transferred from one animal to another with the same exclusion of reaction to foreign material. Thus, the underlying mechanisms of several autoimmune diseases in experimental animals are being defined. This should increase our understanding of the human autoimmune diseases.

PARASITIC DISEASES

The United States is committed actively in global malaria eradication programs. In little more than a decade, these have reduced by half the incidence of this disease, which previously infected 300 million people and killed 3 million annually.

Today, increasing mosquito resistance to insecticides, parasite resistance to drugs, and other problems continue to challenge success in this enterprise. We now must consider simian malaria as a possible factor in the transmission of malaria to man.

To extend investigation of simian malaria into the field, an area of high natural infectivity was needed where it would be possible to study all aspects of the simian-human malaria chain. Field assignments in Malaya begun in the summer of 1960 were so productive that a field station has now been established there. The Far East Research Unit (FERU) is located at the Institute for Medical Research in Kuala Lumpur, Malaya, following negotiations with the Army's U.S. Medical Research Unit and concurrence by the Malayan authorities and the Walter Reed Army Institute of Research.

A significant research finding from FERU is identification of a mosquito that transmits malaria to monkeys in nature. This vector, *Anopheles hackeri*, has been regarded as a rare species, but is now known to be common in one part of Malaya.

The finding that *A. hackeri* is a vector of one of the many kinds of simian malaria marks the first demonstration of a natural vector of monkey malaria. This is an important link in the chain of evidence that may eventually identify the carriers involved in the transfer of the disease in monkeys. The study of relationships between simian and human malarias continues to be an important problem relative to worldwide malaria eradication.

The occurrence of drug resistance in the malaria parasite represents a problem of considerable importance. There were indications of a developing resistance by a Colombian strain of malaria to the widely administered drug, chloroquine, used in eradication programs and in clinical treatment since World War II. This resistance was definitely demonstrated for the first time this year by Institute and University of Texas scientists working collaboratively. Six of seven patients with *P. falciparum* malaria failed to respond adequately or relapsed quickly after normal doses of the drug.

While we must continue to develop an armamentarium of antimalarials, as well as new methods of mosquito control, basic studies of resistance mechanisms also are being undertaken.

In the worldwide campaign against parasitic diseases, schistosomiasis is once again emerging as the major affliction of millions in countries of the Middle East, Latin America, Africa, Europe, and Asia where populations are increasing rapidly.

Our surveys indicate that vast new irrigation projects in some of these countries provide habitats for fresh water snails which are the intermediate hosts for the disease. Apparently, this has been the case in Lebanon, heretofore free of this disease. An Institute scientist took part in an investigation which strongly indicates that a new irrigation project in Lebanon has resulted in the spread of schistosomiasis. These findings give a special urgency to research in this disease.

Institute grantees at Tulane University report the first canine schistosomiasis in the Western Hemisphere. In Louisiana swamps, they found evidence for a well-established host-parasite relationship in a wide range of animals. The extent to which the species, *Heterobilharzia americana*, would develop in man is not yet known.

In addition to basic studies of *Schistosoma*, we are conducting experiments to lead to more effective use of drugs, such as stibophen, against the disease. The power of several compounds to kill *Schistosoma mansoni* can be increased up to 16 times in mice by the administration of a semisynthetic diet. Research on the influence of nutrition on human schistosomiasis is underway in Puerto Rico.

A grant-supported study at the State University of Iowa represents an interesting experimental approach to immunization against schistosomiasis. The rhesus monkey, like man, is not susceptible to infection by the nonhuman strain of *S. japonicum*. The investigators inoculated the monkeys with this strain and found from subsequent challenges with a human strain that a rather strong protection had been provided by the inoculations.

Worm parsites drain the vitality of large segments of the populations in countries linked economically and politically with our own. In regions of the world where human feces are used for fertilizer, vegtables and fruits may be contaminated with infective stages of hookworm and other worm parasites. Although a number of chemicals kill such parasites, no agent has been acceptable for use as a disinfectant of these fresh foodstuffs. A grantee at Tulane University tested easily prepared aqueous solutions of iodine, and found they killed common intestinal parasites quickly on certain items of produce. The application did not alter the quality of these fruits and vegetables.

A new method for preserving live protozoa in cold storage was developed by an Institute investigator in collaboration with naval scientists, using the one-celled *Entamoeba histolytica*, an organism that couses dysentery. This parasite survived cold storing in liquid nitrogen.

INTERNATIONAL RESEARCH CENTERS

The International Centers of Medical Research and Training, established on a continuing long-term basis, enable U.S. physicians and researchers to acquire broad field experience through projects conceived in ample breadth and duration;

and incidentally, to improve the skills of participating foreign scientists; and to encourage further development of public health programs in the interested oversea countries.

The approval of the first application of American universities to sponsor the centers was given in November 1960 under authority of the International Health Act of 1960. The program is being administered by the NIH Office of International Research. Applications are considered by the National Advisory Allergy and Infectious Diseases Council.

The participating American universities provide a stable professional framework in which medical research projects, planning and training can be conducted. Five such universities, and their oversea collaborators are listed below:

The University of California (San Francisco) is collaborating with the Institute for Medical Research, Kuala Lumpur, Malaya.

Johns Hopkins University (Baltimore) is collaborating with the School of Tropical Medicine, in Calcutta, India.

Tulane University (New Orleans) is collaborating with the Universidad del Valle, Cali, Colombia.

The University of Maryland (Baltimore) is collaborating with the Institute of Hygiene, Lahore, West Pakistan.

Louisiana State University (New Orleans) is collaborating with the University of Costa Rica, San Jose.

STAPHYLOCOCCAL INFECTIONS

The danger of staphylococcus going unheeded as a major public health problem is past. The havoc staphylococcal infections cause in the nurseries, general wards and surgical units of our Nation's hospitals is now well documented. Community health dangers caused by discharged patients who have become infected by penicillin-resistant strains of staphylococcus are increasing public concern.

The recognition of these strains has spurred the development of synthetic penicillins resistant to penicillinase, the enzyme which constitutes the major factor in the mechanism of drug resistance. The administration of some of these penicillins has produced dramatic results; but their ultimate value will not be known until they have been in general use for an extended period. An Institute scientist reported this year on an efficient method for preparing cell-free extracts of staphylococcal penicillinase. The method should prove useful wherever this substance is under extensive study.

Our Institute investigators are continuing their successful clinical testing of Dimethoxyphenyl penicillin begun in 1960, and have initiated new regimens with another experimental penicillin developed by Bristol Laboratories. This as-yet-unnamed antibiotic appeared 5 to 10 times more effective than dimethoxyphenyl when tested in vitro in the laboratory. Our clinicians have since treated 15 difficult cases of staphylococcal infection with the new penicillin and have obtained improvement or cure of each patient. Only two patients experienced side effects from treatment, manifested by mild gastrointestinal upset.

Though of obvious importance, the development and testing of drugs is not the final answer to the staphylococcus problem. For example, some 90 percent of our population have these micro-organisms in the nose or on the skin or some other body area at all times. This leads to the perplexing question: why, since we are subject to such great exposure, don't we all become infected? The Institute is supporting studies, therefore, related to host resistance and the basic mechanisms of infection. In our Laboratory of Bacterial Diseases there is continued emphasis in defining factors responsible for virulence of the organism and in developing basic studies of methods for identification of pathogenic strains of staphylococcus.

We are also vitally interested in studies that offer pragmatic methods for the control of hospital-spread staphylococcal infections. A careful procedure for skin care with a well-known antiseptic (hexachlorophene) appears promising for this purpose. Institute grantees report that of 965 infants washed according to the procedure at the Yale-New Haven Medical Center, only 3 percent were found colonized by staphylococcus. In another group of 500 babies subject to the same environment, who did not receive this care, 51 percent were colonized.

CYSTIC FIBROSIS

During the coming year, the Children's Bureau will be collecting data on the extent of cystic fibrosis along the eastern seaboard. The National Center for

Health Statistics is cooperating in this survey, which is financed by a research contract from the National Institute of Allergy and Infectious Diseases. Our advisory council has recommended that the project be limited to the eastern seaboard portion, which should provide an index to the magnitude of this problem. As noted in the record last year, a pilot survey indicated an incidence of 1 cystic fibrosis case in each 2,300 live births, with fatalities extending frequently into childhood and adolescence.

This Institute and the National Institute of Arthritis and Metabolic Diseases share a research interest in this disease. Our grantees at Harvard this year alerted physicians to the importance of considering cystic fibrosis in the diagnosis of patients with recurrent respiratory tract involvement. The grantees reported finding that a large percentage of cystic fibrosis patients had originally been misdiagnosed as respiratory allergy cases.

MIDDLE AMERICA RESEARCH UNIT

This laboratory, a field unit of our Laboratory of Tropical Virology, is operated collaboratively in the Panama Canal Zone with the Walter Reed Army Institute of Research. It has completed its third year of research on fungus diseases and viruses of the tropical rain forests. Some of the scheduled virological activities were deferred during several months of the past year when the scientists at MARU had the opportunity to study at close range an urban epidemic of Venezuelan equine encephalitis, with trials of vaccine under natural conditions of infection. New information on the epidemiology and the clinical spectrum of epidemic infection of this type is now being developed by MARU and the Gorgas Memorial Laboratory in the Republic of Panama. This information is of particular interest because of the sporadic occurrence of epidemics of equine and human encephalitis in regions of the United States.

Studies on the prevalent histoplasmosis fungus have continued. Repeated isolation of this fungus from bat liver and spleen suspensions provide further evidence for the suspected role of bats in the ecology of histoplasmosis.

MARU has expanded into the second and third floors of the former Gorgas Hospital nurses home in the Canal Zone, while its home base facility in Bethesda has been rebuilt into an attractive and efficient modern laboratory.

GORGAS MEMORIAL LABORATORY

The Gorgas Memorial Laboratory, medical research unit of the Gorgas Memorial Institute of Tropical and Preventive Medicine, has been in operation since 1929, when it was established through legislative agreement between the Governments of the United States and Panama. It is an important research center on tropical and parasitic diseases for the United States, Central and South America and other countries of the world. Many investigators from these areas have utilized the laboratory for productive research. The Gorgas staff, itself, is composed of recognized authorities in several fields, most of these scientists have spent the major portion of their professional careers in the tropics.

During the years just before and after World War II this laboratory helped to maintain our position against the tropical diseases, then generally ignored, although representing a growing economic and world health problem.

The projected research program of the laboratory will be a continuation of the present long-term studies on leishmaniasis, trypanosomiasis, malaria, and of yellow fever, and other arthropod borne virus diseases. New projects in experimental pathology, comparative vertebrate zoology and epidemiology, are also planned in new facilities which will be ready for occupancy soon.

One of the major investigations at the Gorgas Laboratory concerns leishmaniasis, a disease prevalent in rural Middle America and found occasionally in the Southern United States. A newly established U.S. Naval Medical Science Unit has also been working with Gorgas on this problem. Recently certain Middle America communities heavily infested with the vector sandflies have been located and human infections studied to determine the most effective chemotherapy of leishmaniasis.

The overall program which has been in progress for 5 years involves several principal phases of the problem, namely: (1) the epidemiology of American cutaneous leishmaniasis in Panama, and to a certain extent in other countries of Central America; (2) testing of drugs, especially those orally administered, such as pyrimethamine, which can be taken in the home by a population for whom medical services are not available; (3) the search for the natural reservoir, which is certainly some forest animal other than man; (4) study of the probable vector, one or more species of Phlebotomus sandflies.

Gorgas investigators have continued their extensive study of arthropod-borne virus diseases of importance to man and domestic animals. In 1961, they reported the first isolation in Panama of Ilheus encephalitis virus from mosquitoes and from two species of birds. This virus is antigenically related to St. Louis equine encephalitis virus, an agent involved in sporadic animal and human outbreaks of the disease in the United States.

Recently, an epidemic of Venezuelan equine encephalitis in Panama has afforded an opportunity for investigators at our Middle America Research Unit (MARU) in the Canal Zone to collaborate with the Gorgas scientists in obtaining important data from this naturally occurring epidemic.

Maj. Gen. Paul H. Streit (U.S.A., ret.), President of the Gorgas Memorial Institute of Tropical and Preventive Medicine, Inc., has submitted a copy of the operating budget for the Gorgas Memorial Laboratory. As spokesman for the Gorgas Institute before Congress, I am requesting that the maximum funds amounting to $250,000 authorized by Congress be made available to the Institute during fiscal year 1963.

THE NEXT 25 YEARS

The National Institute of Allergy and Infectious Diseases continues its strong support of training in microbiology. This is building the manpower potential for research in a number of fields. New and renovated facilities are being established at Bethesda and in the field. Electronic instrumentation and improvements in methods greatly reduce the time needed to complete many laboratory procedures. Development and use of more effective contractual and other cooperate arrangements for completing high-priority research also contribute to greater productivity.

Today, with greater emphasis upon public health and the basic disciplines of microbiology and immunology, there is reason to expect that the next quarter century will witness advances stemming from the work of the National Institute of Allergy and Infectious Diseases as dramatic as the accomplishments of the 75 years for which 1962 is the anniversary.

SUPPORT OF INSTITUTE PROGRAMS

The 1963 request for the National Institute of Allergy and Infectious Diseases is a total of $59,342,000, which provides for about 190 additional research projects as well as increases in direct research, collaborative studies, review and approval of grants, and administration. The request for 1963 is distributed among program activities as follows:

Grants and related contracts:	
Research	$37, 145, 000
Fellowships	1, 610, 000
Training	5, 350, 000
Subtotal, grants and related contracts	44, 105, 000
Direct operations:	
Research	10, 005, 000
Collaborative studies	4, 050, 000
Review and approval of grants	894, 000
Administration	288, 000
Subtotal, direct operations	15, 237, 000
Total 1963 request	59, 342, 000

Mr. Fogarty. Please proceed, Dr. Andrews.

HISTORY OF NIH

Dr. Andrews. I suppose you have been informed repeatedly this year that this is the 75th anniversary of the NIH. It is 75 years old. Of course, our Institute——

Mr. FOGARTY. I do not know if it has been mentioned before or not. Why do you not tell us something about it?

Dr. ANDREWS. It was in August 1887, that Dr. Joseph Kinyoun, a medical officer of the U.S. Marine Hospital Service, returned to this country from Europe where he had been sent to study the new science of microbiology which was being rapidly developed by Pasteur, Koch, Ehrlich, Roux, von Behring, and others. In addition to his new knowledge, Dr. Kinyoun prudently brought back with him a microscope and a few other pieces of European scientific equipment. He set up a small bacteriological laboratory in the U.S. Marine Hospital on Staten Island, N.Y., and proceeded to demonstrate living and stained disease-producing microorganisms—among them cholera vibrios. He thus introduced to the medical profession in this country a new means of diagnosing disease, that is, by demonstrating its cause. He used his laboratory also to solve some of the many other infectious disease problems which beset pioneer microbiologists those days—and so we recognize the activities of Dr. Kinyoun and his Hygienic Laboratory, as it was later known, not only as the forerunner of the NIH—but most especially of this Institute.

That was 75 years ago, and while much has been accomplished since then, we are still trying in our own and many other laboratories, to identify the causes of infectious and allergic sickness with the hope and expectation that such intelligence may prove useful in diagnosing, curing, and preventing these illnesses.

VIROLOGIC RESEARCH

The infections which have proved to be most elusive in yielding firm knowledge of their nature, their interrelationships, and their capacity to produce disease are the viruses, especially those involved in the group of upper respiratory afflictions known as the "common cold" or "upper respiratory disease." It is becoming evident, moreover, that viral agents are also implicated importantly as generators of birth defects, certain types of cancer, neurologic, and possibly even cardiac pathology, and are thus of etiologic significance to the other Institutes concerned with these infirmities.

To implement our intramural interest in this important and most complex group of infectious entities, it has been necessary to develop appropriate diagnostic tests and survey techniques. We have used these during the past year, in conducting comprehensive surveys of viral infections in man, and in making special studies of domestic and commensal animals. Certain of these field and clinical investigations have been continued in collaboration with research personnel of the Bureau of Medicine and Surgery of the U.S. Navy; the D.C. Children's Hospital Research Foundation; the D.C. Welfare Department, and with the other Institutes at NIH.

In addition to observations made on persons naturally infected with viral and other infectious diseases, we have utilized extensively inmate volunteers from Federal penitentiaries—as I mentioned in my testimony last year—to perform rigidly quantitated and controlled experiments testing hypotheses or producing new information not otherwise available. Thus 189 volunteers were inoculated in 1961 with at least one of 14 different viruses or with the Eaton agent, which I shall refer to later. The purpose of these studies is to assess the capacity of these various agents to cause colds or other respiratory illness under strictly controlled conditions. Most of the viruses employed were suspect because they had been associated with epidemics of respiratory disease, but their exact role had not been identified. The volunteers enabled us to get this precise determination in a fraction of the time in which the information might otherwise have been obtained. The studies represent an important advance toward clarifying the entire picture of respiratory disease in the general population. This is the first step in our vaccine development program which I will mention later.

All of the 14 viruses tested this year in the volunteers caused symptoms of acute respiratory disease in varying degrees. They all produced specific antibodies in their recipients. Symptoms appeared also in volunteers who possessed antibodies to the viruses with which they were inoculated, but in such instances the symptoms were uniformly less severe. Illness and virus excretion began the second day after inoculation. In all instances, the test virus was repeatedly present, and could be isolated from the throat and lower intestine as long as 5 or 6 days later, and after recovery from the illness.

In other observations of naturally occurring infections in orphanages and children's hospitals, these same viruses, and related ones, were isolated repeatedly from youngsters with acute upper respiratory disease. Chemotherapy thus far has not altered the course of these infections, though some of the symptoms may be ameliorated temporarily by drugs.

EXPERIMENTS WITH THE EATON AGENT

Six prisoner volunteers were experimentally infected with the Eaton agent, mentioned in my testimony last year. As of that time, it was believed to cause primary, atypical pneumonia. This has been confirmed since then, and the agent has also been shown to produce, in some individuals, nonbacterial, middle-ear infections concerning the cause of which little had been known previously. Further studies have indicated that the Eaton agent is not a virus, as had been assumed because of its filterability, but belongs to a category of subbacterial microbes known as pleuropneumonia-like-organisms—or "PPLOs" in laboratory jargon. This organism is susceptible to treatment with (Lederle) tetracycline antibiotics. Furthermore, it can be grown in synthetic media, suggesting the probability that a prophylactic vaccine can be prepared, and that antigen for use in more rapid diagnostic tests may become available.

Observations in local laboratory and clinical facilities further confirm the impression suggested last year that the agents identified thus far—the total is 98 at present—account for about 60 percent of the severe nonbacterial respiratory infections in hospitalized children.

Productive research by grantees continues on the identification, isolation, and characterization of other viruses suspected or known to cause respiratory diseases in man. Observations relating certain viruses to recurrent respiratory diseases at Salisbury, England, have been confirmed in our grantee laboratories.

In convincing studies conducted by separate, grant-supported teams of investigators in several cities, including Chicago, Los Angeles, and Washington, D.C., respiratory syncytial virus has been regularly recovered from large numbers of individuals afflicted with respiratory ailments. The widespread association of this virus with clinical symptoms, and the negative findings in control subjects without symptoms implicates this agent as one of the frequent causes of contagious respiratory disease in man.

RESPIRATORY DISEASE VACCINES

In spite of the splendid progress made in defining the multiple causes of "colds," we are sure that the entire gamut of upper respiratory infection has not yet been defined; investigations to that end will be continued vigorously. However, we believe that enough progress has been made (1) in identifying certain of the more important agents, and (2) in propagating them in quantity outside of man, so that the time has come when serious efforts should be made to encourage the development and testing of one or more polyvalent vaccines against the proven offenders. This will probably be a costly, laborious, and time-consuming operation but, clearly, such an effort based on accumulating knowledge should be made. Accordingly, this Institute is taking the initiative to speed developmental research on new respiratory disease vaccines, and to improve experimental vaccines already developed. We plan to use the facilities of our own laboratories and clinics, of extramural grant-supported research institutions, of the pharmaceutical industry, and possibly of other governmental agencies.

A six-member Board for Vaccine Development has been nominated to advise the Institute on specific problems to be attacked, on the extent of support necessary, organization of the program, and methods for evaluating and checking results as they become available. Board members are chosen from active research groups in universities and in Government; one member represents the National Advisory Allergy and Infectious Diseases Council.

A special report concerning these plans has been prepared for the committee.

Mr. Fogarty. Thank you, Doctor.

1963 BUDGET PROPOSALS

Your appropriation for fiscal year 1962 is $56,091,000 and the request for 1963 is $59,342,000, an increase of $3,251,000; is that right?

Dr. Andrews. Yes, sir.

RESERVE OF 1962 APPROPRIATIONS

Mr. Fogarty. The reserve for savings is $372,000.

Mr. Seggel. That is the directed reserve. The total, including the amount we volunteered, is $973,000.

Mr. Fogarty. This $372,000 is less than 5 percent of the increase Congress appropriated for 1962. I notice some of the other Institutes had well over 20 percent of their increases taken away from them. What kind of a formula was followed in dividing the total reserve up among the Institutes?

Mr. Seggel. Mr. Chairman, this was based on projections we made last summer on the regular research grants and is also based on our estimate of where such programs as the clinical center grants programs were going. In other words, this was done selectively, based on activities in specific programs, within the Institutes.

There is no formula.

Mr. Fogarty. It was not an across-the-board cut?

Mr. Seggel. No, sir. It was an attempt to do the best we could on the basis of the projections we made at that time.

Mr. Fogarty. And you were able to get away with it at the Department level?

Mr. Seggel. The Department gave us the freedom to make those decisions, yes, sir, within the direct operations and within grants.

Mr. Fogarty. You did pretty well, Dr. Andrews, considering the overall cuts made by the Department.

What are you cutting back to save this $372,000?

Mr. Seggel. The cuts were made as follows: $28,000 in research grants, $90,000 in fellowships, $50,000 in training, and $204,000 in the direct operating funds.

Mr. Fogarty. Taking out the nonrecurring construction item for 1962, you have an increase for 1963, over what you are being allowed to spend, of about $5 million. The two main items of increase are $2,448,000 for research grants and $2 million for collaborative studies; is that right.

Mr. Seggel. Yes, sir.

FINANCING RESEARCH APPLICATIONS

Mr. Fogarty. You expect to have over $2,200,000 in approved, but unfinanced, research applications at the end of 1962, so about all this increase will do is finance the backlog that is going to be carried forward from 1962; is that right?

Mr. Seggel. I did not follow that, Mr. Fogarty.

Mr. Fogarty. You expect to have over $2,200,000 in approved, but unfinanced, research applications at the end of fiscal year 1962?

Mr. Seggel. Yes, sir.

Mr. Fogarty. About all this increase will do will be to finance that backlog.

Mr. Seggel. We can finance $2,810,000 in new projects in 1963, leaving $4,915,000 not financed in 1963 in the President's budget.

Mr. Fogarty. Your increase for research grants is just about equal to the amount you will not be able to finance in 1962?

Mr. Seggel. It is about $600,000 more.

Mr. Fogarty. Either we are wrong or you are wrong. My figures are an increase in the 1963 budget of $2,448,000 for research grants and you expect to have over $2,200,000 in approved grants that you won't be able to fund in 1962. Are my figures wrong?

Dr. Andrews. We will have more than that, I believe.

Mr. Seggel. I am looking at this table. I am not sure where the discrepancy is, sir. I'm referring to the amount for new projects in 1963, and excluding those carried over from 1962.

Mr. Fogarty. You can straighten it out for the record.

(The requested information follows:)

Mr. Fogarty is correct in stating that there is an increase of $2,448,000 for the research grants activity in 1963, an amount slightly more than the anticipated unfunded regular research projects in 1962, $2,228,251. However, the increase of $2,448,000 is actually a net increase composed of a gross increase of $4,486,000 (of which $3,787,000 is for regular research projects, and a gross decrease of $2,038,000, a nonrecurring amount reflecting the adjustment of the International Centers for Medical Research and Training. Therefore, in terms of gross amounts, there is an increase of $3,787,000 for regular research projects in 1963 as contrasted to $2,228,251 representing the anticipated unfunded regular research projects in 1962.

COLLABORATIVE STUDIES

Mr. Fogarty. The requested increase for collaborative studies would just about double that program. Tell us what you are doing now and what you plan for 1963.

Dr. Andrews. These collaborative studies are to support the vaccine development and also another program which we are starting this year in preparing viral diagnostic reagents.

Few of the reagents used in identifying viruses are commercially available. They have been prepared in the past in small quantities by individual virologists primarily for their own use. This painstaking process consumes valuable research time. Some of these biologics have been exchanged, tested, and used by others, and this has not infrequently resulted in demonstrating that the materials are not always of comparable specificity, concentration, and quality.

To bring efficient method and product dependability to this area, this Institute is developing a coordinated program to provide standardized reference reagents for qualified virologists of improving and enhancing virologic research. These reagents will be available to all the Institutes whose investigators need them. It is believed that Government coordination will help assure the standardization of these materials and foster comparable nomenclature regarding them. The virus reagents will include certain of the respiratory, enteric, anthropod-borne, pox, and other viral disease groups. Certification will be accomplished by an independent laboratory which will conduct tests indicating whether or not designated standards have been met.

Like the vaccine development project, this program also will be guided by nongovernmental, consultant scientists eminent in the various virologic specialties concerned, plus staff representatives of interested Institutes. Close liaison will be maintained with the Communicable Disease Center, and international groups, such as the World Health Organization. A special report on this proposed activity has been prepared for this committee.

Dr. Shannon. Could I comment on this? It is not commonly understood. Most medical research that has its base on chemicals is highly standardized. Highly purified chemicals are available from a variety of commercial sources but in this field, which has developed very rapidly, there is no biological counterpart to the large chemical house that produces standardized, pure chemical reagents. It is as important to have pure reagents, with known and constant characteristics, for virological research as it is to have pure chemicals for chemical research. What is happening now is that this Institute is providing such reagents because they are esssential to rapid progress in the field. There is beginning to be a somewhat similar need for other types of biologicals such as, for example, genetically purebred experimental animals for which there is no commercial source. Over the next few years there will be an increasing need for standardized materials of this kind built up as a normal and absolutely essential requirement for certain types of biological research. These are very costly reagents. The necessity of making them available is an inevitable consequence of the support of the work. The work cannot go on without these reagents.

CHEMOTHERAPEUTIC TREATMENT OF VIRAL DISEASE

Dr. Andrews. May I say a word about a new area of viral activity which has just occurred? I think that your office is familiar with it, but for the record I would like to state that we regard the successful chemotherapeutic treatment of a viral disease as a breakthrough of fundamental importance.

In connection with viruses, a new development of compelling interest has just occurred. At a scientific meeting only a few days ago in New York, announcement was made of the successful chemotherapeutic treatment of a viral disease. This is a breakthrough of fundamental significance; as far as I know, it is the first time a true viral disease has been successfully attacked by medication.

The disease involved was the ocular manifestations which sometimes appear in herpes simplex, the most common symptoms of which are fever blisters, or cold sores. This is a viral disease.

The drugs used were 5-iodo-(or bromo)-2-deoxyuridine. The theory of their action is that they inhibit the formation of DNA (desoxyribose nucleic acid), an essential constituent of viruses.

Sixty-one infected rabbits were treated, all of whom were cured in 2 days; 132 untreated controls retained their infections for longer periods.

This treatment was given to 46 patients, all the acute cases of whom were satisfactorily cured as far as their ophthalmic symptoms were concerned.

This work was reported by Dr. Herbert E. Kaufman of the University of Florida at Gainesville. The observations on rabbits and man were made at the Massachusetts Eye and Ear Infirmary.

This achievement may well prove to be the open sesamé to the field of viral chemotherapy.

Mr. Fogarty. I read quite a bit about that in the papers within the last 3 or 4 weeks.

Was this drug not first discovered by the Cancer Chemotherapy Program?

Dr. Andrews. That is correct.

Mr. Fogarty. I think this is a real good example of the value of basic research. Even though these drugs are developed in another Institute, they are found to be effective on this disease of the eye.

Dr. Andrews. This is true.

Mr. Fogarty. You gave examples last year of some of the work you are doing in the virus field that the Cancer Institute would use.

Dr. ANDREWS. I understand parenthetically that opthamologists are having trouble in obtaining enough of this drug to take care of the corneal opacities which are the most common eye defects among their herpes patients.

Mr. FOGARTY. What do you think should be done about it?

Dr. ANDREWS. I think that much will be done about it because this is the first time that anybody has managed to make any appreciable effect upon a viral disease with the chemicals.

Mr. FOGARTY. I meant in getting the necessary amounts.

Dr. SHANNON. I think that will be taken care of by normal commercial channels. This is such a new observation that the commercial producers of the drug have not had time to react to the need.

Mr. FOGARTY. Is it different than streptomycin was 15 years ago?

Dr. SHANNON. As a matter of fact, it is a much simpler thing. There won't be any great problem, I believe, in satisfying the demand.

Dr. ANDREWS. We will make continued efforts in this Institute, of course, to follow up on the leads which this provides.

Mr. FOGARTY. Has this ever been tried in the case of shingles?

Dr. ANDREWS. This is another disease under the same genetic name, Herpes, but another kind of disease. I would hazard a guess that it probably would not respond to this. The reason that ocular herpes simplex responds, and you must understand it is only the eye lesions—not the lip lesions—that do respond, is because the lens of the eye is nonvascular and does not have the cellular and metabolic dynamics going into it all the time, which might interfere with the destruction of ribose nucleic acid, which is the basis of the success of the treatment in this idea.

Mr. FOGARTY. Do shingles sometimes affect the eyes?

Dr. ANDREWS. I am not aware they do. Possibly they do, because they cause extensive lesions all over the body.

Mr. FOGARTY. It is a very disagreeable thing.

Dr. ANDREWS. Indeed they are.

Mr. FOGARTY. Please proceed, Doctor.

I did not mean to interrupt.

STAPHYLOCOCCAL RESEARCH

Dr. ANDREWS. I would like to say a little bit about staphylococcal research.

Advances in the treatment of staphylococcal infection continue. Last year I called your attention to the development of a new variant of penicillin, now known by the Bristol Laboratories trade name of Staphcillin and the generic name of Methicillin. This resisted the antipenicillin action of the Staphylococcus enzyme on penicillin G, the type previously used, by a factor of 200 to 1. Since then, the same commercial producer, the Bristol Laboratories, has developed an even more effective product recently released by the Food and Drug Administration. The trade name given to it is Prostaphylin and the proposed generic name in Oxacillin-isoxazolyl penicillin. Its unique quality is its even greater resistance to degradation by penicillinase. It has the further advantage of being administrable by mouth.

Our clinicians have used the new product on 15 difficult cases of staphylococcal infection, and this preliminary clinical trial was favorable, with apparent cures or marked improvement, and only minimal side effects. However, only long usage under a great variety of conditions can confirm these findings and prove the absolute value of this drug.

A special report for the committee has been prepared on "Staphylococcal Infections."

Extramurally, we are continuing our grant support of over $2 million for research on the fundamental nature, the host-parasite relationships, the epidemiology, the management and the prevention of staphylococcal infections.

Among other things, this has produced the somewhat surprising discovery that the early and continuing presence of staphylococci in the nasal mucosa of the newborn can be prevented in a high percentage of cases by repeated washing of the infant's body with the skin disinfectant, hexachlorophene. This study provides valuable information concerning the method by which staphylococci normally spread, becoming established first on the skin and then transferred to the nose by the random movements of the infant's hands, rather than by spread directly into the nose from the air.

Perhaps the most important byproduct of the studies of staphylococcal ecology and control in hospitals to date is the finding that wide variations exist among these establishments in their operation, and that the introduction of control measures highly successful in one hospital do not necessarily improve conditions in another.

Mr. FOGARTY. Why?

Dr. ANDREWS. Because of their different causes, different methods of operating the hospitals, hospital management, I would say.

Mr. FOGARTY. Of course, we should not have that kind of management operating the hospitals.

Dr. ANDREWS. Variations do exist.

Mr. FOGARTY. I know. What can we do about it?

Dr. ANDREWS. Sir, surveys should be made of each individual hospital and then it would be known what is wrong with the particular institution being dealt with and the proper means to be taken to get rid of these deficiencies. We have made a special report for the committee on staphylococcal infections.

Mr. FOGARTY. We will put your special report on this subject in the record.

(The report follows:)

SPECIAL REPORT: STAPHYLOCOCCAL INFECTIONS

Prior to the fall of 1960, there was no generally satisfactory drug treatment for a patient badly infected with penicillin-resistant strains of *Staphylococcus*. Although there are now several greatly improved drugs, they do not constitute the complete answer to the serious public health problem caused by staphylococcal infections.

The successful results of clinical tests of Bristol Laboratories' dimethoxyphenyl penicillin, for example, were characterized during a recent Institute clinical staff meeting by the National Institute of Allergy and Infectious Diseases as "a battle won." It was added, however, that "the war goes on."

Staphylococci are abundant in our society; probably 90 percent of the people have staphylococci on the skin or nose or some other area at all times. This leads to the perplexing and curious problem of why everyone does not become infected. Conversely, it is not known why some individuals are extremely susceptible to severe infections which subsequently can be controlled only by long and costly chemotherapy, or may even have a fatal outcome.

It is difficult to predict by clinical or laboratory means what will happen to a person infected by staphylococci because disease caused by this microbe can range from a simple carrier state to general "blood poisoning" and death.

Staphylococci stimulate very few measurable defense mechanisms in the body, and those which are stimulated, and can be measured, are difficult to assess with regard to their importance in aiding the host to eliminate infection.

These three characteristics alone make it virtually impossible to design a predictably successful therapeutic regimen.

There are many aspects of the problem that demand further study, but until recently there was a dearth of basic research in staphylococcal disease. With the awareness and support of Congress, this Institute has been able to expand basic staphylococcal studies in the intramural research program and to accelerate its grants program to support 104 staphylococcal research projects totaling $1,892,285.

INTRAMURAL RESEARCH

Institute scientists continued during the year to obtain good clinical results from the administration of dimethoxyphenyl penicillin. They also initiated clinical trials of another experimental penicillin resistant to the enzyme—penicillinase—which constitutes the major factor in the mechanism of drug resistance. In addition to offering the distinct advantage of oral administration, this as-yet-unnamed Bristol Laboratories' antibiotic appeared 5 to 10 times more effective than dimethoxyphenyl penicillin when tested in vitro in the laboratory. Treating 15 difficult cases of staphylococcal infection, our clinicians have obtained cures or marked improvement and have observed only minimal side effects.

Such drugs are necessary for the treatment of intractable staphylococcal infection and make continued development and testing obligatory, but only long usage can prove their absolute value. There is always the possibility that bacteria will develop resistance against these new drugs and that individuals will develop allergic reactions to them.

Meanwhile, basic studies are making gains. Laboratory observations make probable the identification of penicillinase as a cyclic peptidase. Such an identification is necessary for even a partial answer to the question of the role and function of penicillinase in nature, and, more simply, to explain why a staphylococcal cell should possess such an enzyme. An Institute scientist this year reported on an efficient method for preparing cell-free extracts of staphylococcal penicillinase. The method should prove useful wherever this substance is under extensive study. Important beginnings were made in the understanding of the biology of staphylococci. Laboratory discoveries about the metabolism of the bacteria extend the hope that invaling staphylococci can be rendered less toxic by juggling their supply of iron nutrients.

Other Institute investigations are aimed at developing a set of standardized tests for grading the relative virulence of various strains of staphylococci. Standardization tests are prerequisite for any future immunization tests. The antigenic mosaic of standard reference strains of *Staphylococcus* has been characterized. The techniques used may lead to a system for identifying pathogenic strains of the organism.

EXTRAMURAL RESEARCH

Many of the Institute's grant-supported projects also concern the fundamental nature of the *Staphylococcus* and its host relationships. Studies at the University of Minnesota Medical School may help clarify the interaction of microorganism and host. This work strongly suggests a precise, or selective, role for alpha toxin (the powerful necrotizing agent produced by *Staphylococcus*) in abcess formation. Interactions of *Staphylococcus* and other organisms are also being studied by grantees. It has been observed by Drs. W. W. Arndt and R. E. Ritts of Georgetown University Schools of Medicine and Dentistry that the *Proteus* organism becomes lethal for laboratory mice when mixed with *Staphylococcus*. The finding opens the possibility for study of this phenomenon in natural infection. Clinicians report that *Proteus* infection is a considerable problem in the hospital.

More than one-third of the grant-supported projects are related to the jeopardy imposed on the Nation's hospitals by staphylococcal infections. Patterns are degrees of staphylococcal infection are not equal in all hospitals. If a nationwide program of control of infection in hospitals is to be established, however, it will derive only from a compendium of successful individual experiments. From such a pooling of research intelligence it should be possible for institutions with refractory problems to draw upon the techniques which brought staphylococcal infections under control in similar circumstances. Projects in this category, therefore, are attempting to identify and control the sources of infection and the means by which patients become infected.

Drs. Louis Gluck and Harrison F. Wood, Yale-New Haven Medical Center, recently reported they virtually eliminated staphylococcal nasal colonization of newborn infants by following a carefully designed method of hexachlorophene washing. Their study was intended to challenge the findings of a similarly successful grantee experiment at Palo Alto-Stanford Hospital with which Dr. Gluck was associated. They report that of 965 infants washed according to the method at the Yale-New Haven Center, only 3 percent were found colonized by *Staphylococcus*. In another group of 500 babies subject to the same environment, who did not receive this care, 51 percent were colonized.

In addition to pragmatic findings, the study suggests a new epidemiological route by which nasal colonization of infants by staphylococci may occur. Staphylococci are introduced into the nursery by the many environmental factors described by previous investigators but, according to the Yale scientists, staphylococci colonize the umbilical cord and skin of newborn infants first. They may then be borne into the nose chiefly by the infants own random hand movements. In other words, the study indicates the individual infant's greatest danger is himself. The Yale investigators interpretation of the marked effectiveness of their hexachlorophene washing technique is that it prevents the first step of skin and cord colonization.

One of the Institute's larger staphylococcal projects—a long-term cooperative study by five medical schools to test the efficacy of ultraviolet radiation in preventing postoperative wound infections—is entering its final year. George Washington University, Hahnemann Medical College, University of California, University of Cincinnati and the University of Pennsylvania are submitting data to the National Academy of Sciences for statistical analysis. A most important byproduct of this study is the accumulation of vitally important information relative to surgical wound infections in general.

Mr. Fogarty. Are you satisfied with the progress you are making in this area?

Dr. Andrews. Yes. I think it has been pretty good, considering the difficulty of the general area that is involved.

CYSTIC FIBROSIS

May I say a word about cystic fibrosis?

Mr. Fogarty. Yes. We are interested in that.

Dr. Andrews. Our interest in this tends to diminish a little because as we improve the staphylococcal treatment of infections, this becomes less and less of a problem in cystic fibrosis, because the deaths which occur in cystic fibrosis are usually due to staphylococcal pulmonary infections.

We know that you are interested in the distribution and occurrence of this disease and, as I have testified here before, we have supported the Children's Bureau by means of research contracts to make surveys of this disease in different parts of the country. The last one was made in certain of the New England States and a preliminary estimate of the incidence of diagnosed cases is 42 per hundred thousand live births, or 1 per 2,300, a lower estimate than that given for the population in general. By and large, cystic fibrotic children are living longer because they are getting better care and so their life expectancy has been increased materially.

Incidentally, some of our Harvard grantees found that a high percentage of cystic fibrosis patients were misdiagnosed as having respiratory allergy, and they also showed that the reverse had occurred, that there was masked—and therefore untreated—respiratory allergy in what were actually cystic fibrosis patients.

MALARIA RESEARCH

You may recall that I announced in my testimony last year the initiation of a new area of research in the field of malariology. Scientists in our Institute succeeded in transmitting malaria from certain Malayan monkeys through *Rhesus* monkeys to man. This finding was speedily confirmed by one of our grantees, and was also observed in a third laboratory where research on the same strain of simian malaria was in progress. This is important because of the questions it raises concerning the eradication of malaria.

Developments since that time include the acquisition of modest laboratory space at the Communicable Disease Center in Atlanta in which to work with mosquitoes and monkeys. This was sought because of the obvious advantage of having monkeys, mosquitoes, and laboratory working space reasonably near the Atlanta Federal Penitentiary, where most of the inmate volunteer infections are produced. Man-to-mosquito-to-man and man-to-mosquito-to-monkey transmissions have both been accomplished consistently and repeatedly with two strains of monkey malaria (*Plasmodium cynomolgi.*) There can be no doubt but that the parasites of this natural infection of Malayan monkeys can be made to live in man. To determine whether or not this also occcurs spontaneously in human natives, is the mission of a newly established field laboratory, the Far East Research Unit (FERU), which has been located in Kuala Lumpur, Malaya, to study the surrounding simian, mosquito, and malaria-parasite faunas, their mutual ecologic relationships, and the transmissibility of simian malaria to man under natural conditions.

The following observations have been made to date:

1. Seven species of Malayan *Anopheles* mosquitos have been shown capable of transmitting simian malaria in the laboratory. None of these vectors were known prior to the establishment of the FERU.
2. *Anopheles hackeri*, an indigenous forest species, has been found infected in nature with sporozoites which produced *cynomolgi*-type malaria when injected into monkeys.
3. Several species of monkey-malaria parasites, two of them previously unknown, have been found. These two new species have been described and named after prominent malariologists.

It is to be emphasized that the findings thus far demonstrate only that malaria can be transmitted to man by monkey under laboratory conditions. It has not been proved thus far that it is ever transmitted from monkey to man in nature. This, if true, remains to be ascertained.

Some of our grantees have studied the natural occurrence of malaria in monkeys in Pakistan. Others including our intramural as well as extramural scientists—have found that monkey malaria increases its adaptability and virulence for man on repeated passages through human hosts.

Interesting observations have been made recently on the immunology of malaria. No practical serologic test for antibody detection has been available until this year when our immunologic and malariologic scientists were able to adapt the fluorescent antibody technique to show beyond doubt that malaria antibodies are produced. Working with the blood of infected human volunteers, it has been possible not only to detect antibodies but to measure their quantitative occurrence, and to correlate this with the appearance and number of parasites. These observations, which have been made from the blood of patients with human and with simian malaria, provide both a novel and practical method for diagnosing malaria, and a new technique for studying the disease and its host-parasite relations.

This, I think, may be of great importance as it could conceivably lead to some sort of mechanical or perhaps electronically activated contrivance to be used in making malaria diagnoses.

TRAINING AND FELLOWSHIP PROGRAMS

Mr. Fogarty. You do not have any increase for training or fellowships, do you?

Dr. Andrews. That is correct.

Mr. Fogarty. You do not mean to tell me that you have run out of potential candidates for fellowships, do you?

Dr. Andrews. We will have candidates next year as we had this last year, I suppose; yes, sir.

Mr. Fogarty. It is not a question of shortage of personnel that could be trained?

Dr. Andrews. I think it is always possible to increase interest in the field of this kind.

ROCKY MOUNTAIN LABORATORY

Mr. Fogarty. You received last year $750,000 for construction at your Rocky Mountain Laboratory. How is that progressing?

Dr. Andrews. The construction is well underway, I am happy to say. The building will be rehabilitated. An excellent insectary is being built within it, a laboratory for dealing with "hot" agents is being constructed, along with new animal facilities at the Rocky Mountain Laboratory.

Mr. Fogarty. What is the nearest city of any size?

Dr. Andrews. The Rocky Mountain Laboratory is situated in Hamilton, Mont. This might not qualify as a city of great size, Missoula is the nearest, large city.

Mr. Fogarty. You can get in and out by plane?

Dr. Andrews. Yes, sir. One goes to Missoula and then by automobile to Hamilton, about 40 miles.

Mr. Fogarty. Are you planning any expansion of activities at that laboratory in 1963?

Dr. Andrews. Investigations have continued in our Montana installation with the same general objectives as in the past, oriented toward the zoonoses, arthropod-borne diseases, and problems related to immunity.

An isolation of Powassan virus from ticks in western South Dakota has resulted in intensified ecologic studies in this area, with the consequent finding of antibodies in sera from local chipmunks and wild mice. A human serum from western Minnesota and one from central

North Dakota—of 1,058 miscellaneous samples tested—showed high neutralizing indexes against this virus. Regional field work will be focused on ecologic and public health aspects of this virus, in view of the known significance of the related Russian spring-summer encephalitis.

As a result of the funds—$750,000—provided in 1962, work has been started to modernize buildings and construct new animal facilities at the Rocky Mountain Laboratory. Among the new structures will be an insectary and an isolation building for work on highly infectious disease agents. The laboratory at Hamilton, Mont., has grown from a regionally important facility to become an important center for medical research on national and world health problems as well as those of special interest to our Western States.

OTHER FIELD STATIONS

Mr. Fogarty. You also have field stations in Hawaii, Puerto Rico, Malaya, and Central America. Are there any others?

Dr. Andrews. I think you have about called the roll, though this Institute has no installation in Puerto Rico.

Mr. Fogarty. I just happened to notice your justifications mentioned some work you had done there.

We were disappointed last fall not being able to get down to Central America after we put you to a lot of trouble.

Dr. Andrews. I have just returned from a visit to Panama.

Mr. Fogarty. It was my fault. I could not get away at the time. I think our committee ought to take a look at these stations sometime in the near future.

Dr. Andrews. You may be interested in knowing that there is a new president of the Gorgas Memorial Laboratory, whose name is Dr. Paul Streit.

Mr. Fogarty. I think he is going to appear as an outside witness. What do you have in Hawaii?

Dr. Andrews. In Hawaii it is a very modest affair. You see, during the last 18 months, one of our staff scientists who studied extensively in the Pacific Islands, recognized a brandnew disease.

Mr. Fogarty. Please proceed, Doctor.

Dr. Andrews. We have a couple of rooms in the Queens Hospital, Honolulu, with one professional and I suppose a couple of technicians who will provide facilities for the investigation of this disease. This is a cerebro-spinal meningitis which is a curious condition. It is caused by a worm parasite which occurs naturally in the lungs of rats. How this parasite gets into the nervous system of man is a mystery still to be explored. The laboratory will concern itself with this and other diseases, including viral ones of particular importance in the Hawaiian Islands and in the Pacific area. After 2 or 3 years this program will be evaluated to determine whether it should be continued or altered.

Mr. Fogarty. We will insert in the record your special statement on work in Central America.

(The statement referred to follows:)

MIDDLE AMERICA RESEARCH UNIT

The fourth year of the existence of this establishment has seen the continuation of field-laboratory investigations on viral disease in the Panama Canal Zone with supportive laboratory studies in Bethesda, both operated directly by this Institute. In addition, a more limited program on mycologic research at the Middle America Research Unit is supported by the Walter Reed Army Institute of Research.

The first isolation of Venezuelan equine encephalitis (VEE) virus in Panama was accomplished in April from specimens obtained from a dying Panamanian boy from Canito. Three senior laboratory staff members became infected as a result of the exposure. Following this episode, the entire Middle America Research Unit contingent, and members of the Gorgas Memorial Laboratory who might be exposed, were immunized with live, attenuated VEE virus vaccine. Mild reactions were frequently encountered, and attenuated virus was isolated from some of the vaccinees. Several aspects of the practical application of this experimental vaccine were thus explored.

Epidemiologic and ecologic studies of the rural community where the first recognized case had occurred (made jointly with the Gorgas Memorial Laboratory) failed to demonstrate Venezuelan equine encephalitis virus in wild, domestic, or sentinel animals, or in the mosquitoes collected locally. Nevertheless, serologic evidence of Venezuelan equine encephalitis infection was established for a significant percentage of residents of the area.

Another new study now underway is developing information about the vesicular stomatitis virus of the Indiana type, which has been isolated repeatedly from Panamanian sandflies.

The first human case of actinomycosis (cervical-facial type) caused by *Actinomyces bovis* was diagnosed and recorded, demonstrating for the first time the presence of this disease on the Isthmus of Panama. (This is a fungal disease of cattle—sometimes transmitted to man—characterized by granulomatous lesions which form abscesses, sinuses and tissue destruction—called lumpy jaw—infectious to man.) The probable role of bats in the transmission of another fungal disease—histoplasmosis—was emphasized by the repeated isolation of the fungus from their livers and spleens. This is a new and important observation.

Other activities of the Middle American Research Unit have involved the characterization of arbor-viruses in tissue culture, the development of experimental procedures to improve serologic detection of these viruses, studies on the attraction and feeding behavior of arthropod vectors of viral diseases, epidemiologic investigations and surveillance in Panama and Central America, viral jungle fever in U.S. military personnel and studies of microbial diseases of military importance in Latin America.

As I mentioned last year, one of the main deterrents in the past to the effective use of the Middle America Research Unit facility has been lack of housing for personnel in the Canal Zone. Eleven housing units now are being constructed. A cooperative arrangement for use of building plans and maintenance facilities is being worked out with the Federal Aviation Agency, which just completed housing units in this area for its employees.

GORGAS MEMORIAL LABORATORY

The Gorgas Memorial Laboratory, established in 1929 by legislative action of the Congress of the U.S.A. and the Republic of Panama, and supported largely by U.S. congressional contribution, has experienced a highly productive year. This laboratory is the operating agency of the Gorgas Memorial Institute of Tropical and Preventive Medicine, Inc., and was activated to study diseases of the American tropics. It is located in the Republic of Panama, a few miles from our Middle America Research Unit in the Canal Zone. The combined specialized expertise, facilities, and connections of these two laboratories have made possible certain collaborative research enterprises which probably would not have been undertaken by either alone.

The Gorgas Laboratory was also involved with the Middle America Research Unit during 1961 in the studies of Venezuelan equine encephalitis (VEE). The virus of this disease of man and horses was isolated during the year from hospital patients with febrile illnesses of unknown origin, from mosquito collections, and from laboratory workers presumably exposed to infectious material.

Epidemiologic investigations were made in and around the town of Almirante, where it was found that a brief epidemic of a febrile illness of unknown origin had occurred in June. As a result, the Gorgas Memorial Laboratory was able to reconstruct the genesis and development of this disease. In April, at the time of death of the first recognized case of Venezuelan equine encephalitis in Canito, the virus of VEE was present in the mosquitoes near Almirante. In May, the virus was also recovered from wild ground mammals nearby. In June, the human epidemic began in the urban population.

The Gorgas Memorial Laboratory has continued its grant-supported investigations of the ecology of arthropod-borne viruses in the tropical rain forests of Panama, in collaboration with the Middle America Research Unit. Prodigious numbers of arthropods and native vertebrates have been collected and examined virologically or serologically. A general picture of the wild reservoirs, vectors, and hosts of viral infection is gradually emerging.

Malaria is also under study. Antimalarial drugs, used in mass medication, appear to have successfully halted transmission of the disease in the study area. Very extensive work on leishmaniasis has revealed information about the natural history of the sandfly vectors of this disease. Variations in pathogenicity for certain Leishmania strains have been shown. Our Rocky Mountain Laboratory is beginning to collaborate with Gorgas Memorial Laboratory in studies on the sandflies and other biting arthropods. The U.S. Naval Medical Science Unit assigned to the Gorgas Laboratory is also cooperating in research on leishmaniasis and other infections, including Chagas disease.

The construction of additional facilities at the Gorgas Laboratory was started this year with the $500,000 made available for this purpose by Congress in 1961. An animal production building is already completed and new laboratory space is being built. This should be finished by the end of this calendar year or early in 1963.

The Annual Report of the Gorgas Memorial Laboratory for 1961 was issued recently. This sets forth a very impressive record of scientific achievements during the year. I will be glad to obtain copies for those here desiring them.

The members of this subcommittee who have special interests in the Gorgas Memorial Institute and Laboratory will doubtless be interested and pleased to hear of the recent election of Dr. Paul H. Streit as president of the incorporated Institute. Dr. Streit is a retired major general, U.S. Army, and has had responsible assignments at most of the larger medical installations in this country, as well as duty overseas. For 4 years, he was Commandant of the Army Medical Center and the Walter Reed General Hospital. He is presently the clinical consultant for the United Mine Workers welfare and retirement fund.

Again, I have the great personal satisfaction of recommending to the Congress that the work of this laboratory be supported next year, as it has during the past, by a contribution of $250,000. It is increasingly evident that the opportunities for infectious and parasitic disease research in middle America will exceed the combined facilities available at the Gorgas Memorial Laboratory and the Middle America Research Unit for the foreseeable future.

INTERNATIONAL CENTERS

Mr. Fogarty. Was it not your Institute that started the first International Center?

Dr. Andrews. Yes, sir.

Mr. Fogarty. Tell us something about it.

Dr. Andrews. At present there are five of these International Centers in existence. These were established, to provide novel opportunities for the training of research workers under circumstances which could hardly be duplicated in this country. Each of these centers consists of an American university—a medical school or center to whom the grants are made, and these, in turn, have affiliates overseas.

Mr. Fogarty. Where did you say it was located?

Dr. Andrews. The grants are all made to American universities, but they have affiliates overseas in different parts of the world. The expenses of the affiliate are paid by the grantee institutions.

Mr. Fogarty. Tulane was one, was it not, and the University of California.

Dr. ANDREWS. LSU is another.

Dr. SHANNON. The University of California, Hopkins, and Maryland.

Dr. ANDREWS. Those are the other three.

Dr. SHANNON. There is a very brief report on those.

Mr. FOGARTY. Let us put it in the record.

(The document requested follows:)

SPECIAL REPORT: INTERNATIONAL CENTERS FOR MEDICAL RESEARCH AND TRAINING

The program for International Centers for Medical Research and Training (ICMRT) was established by the National Institutes of Health in November 1960 to advance a major objective of the International Health Research Act of 1960 (Public Law 86–610). This objective is the broadening of collaborative research and research training between U.S. and foreign institutions and investigators.

The ICMRT instrumentality represents a new departure in NIH programing, assuring greater continuity and stability in projects covering specific areas of reciprocal and collaborative research on an international basis. A major advantage of this program is that it provides opportunities for highly competent U.S. scientists to exploit unusual research opportunities abroad and to obtain valuable experience in a foreign setting without losing their valuable university connections. Applications for ICMRT grants are received by NIH from American universities and are subject to regular scientific and program review and approval procedures. With grant approval the universities establish centers within their own organizations which provide a stable professional framework within which medical research projects, planning, and training may be conducted. At the same time the universities negotiate with foreign institutions to establish affiliate centers which will have the necessary research facilities and scientific and technical competence to support the research programs agreed upon. These collaborative research and training centers abroad offer both U.S. and host country investigators environmental, ethnic, and medical conditions unavailable in the United States. Furthermore, the research training provided in connection with these activities will increase the number of individuals competent in this important area. The institutions at present involved, and their respective programs are as follows:

University of California Schools of Medicine and Public Health, and the Hooper Foundation in collaboration with the Institute for Medical Research, Kuala Lumpur, Malaya.

The research program is initially centered on anthropod-borne virus diseases, mycology, endocrinology, parasitology, and entomology with training emphasis in the fields of endocrinology-metabolism, biochemistry-immunology, microbiology-virology, geographic pathology, and medical ecology.

Johns Hopkins University School of Hygiene and Public Health and Department of Medicine in collaboration with the School of Tropical Medicine, Calcutta.

The research program has primary interests directed to the fields of pathobiology and general medicine, with emphasis on hematologic, infectious, neoplastic, and nutritional diseases.

University of Maryland School of Medicine in collaboration with the Institute of Hygiene, Lahore, West Pakistan, and other cooperating institutions in the area.

The general research program has emphasis centered initially on fevers of unknown origin, gastrointestinal infections, parasitology, pulmonary disorders, nutrition, pediatrics, preventive medicine, and epidemiology.

Tulane University School of Medicine in collaboration with the Universidad del Valle, Cali, Colombia.

The research program is directed primarily to studies on fevers of unknown origin, enterobacteria and shigella, tuberculosis in children, mycotic diseases, general virology, nutrition, cardiovascular diseases, hematology, cysticercosis, demography, sociology, and maternal and child health.

Louisiana State University (New Orleans): The faculty of the school of medicine is pursuing studies in Central America.

The overall research approach will include studies in virology, bacteriology, parasitology, mycology, metabolism, biometry, and pathology of chronic diseases, such as cancer and vascular diseases.

ADMINISTRATION OF THE PROGRAM

In fiscal year 1962 the funds for support of the international centers and other special international programs were supplied by appropriations to the Institutes (except Dental Institute) and the Division of General Medical Sciences. The Institutes then allocated funds to the National Institute of Allergy and Infectious Diseases for the support of the ICMRT program. In fiscal year 1963 the administration of the ICMRT program will be handled centrally by the new Office of International Research through the appropriation entitled "General research and services" which supports the Division of General Medical Sciences. The Advisory Committee for the ICMRT program will continue to operate as before except that it will now report to the National Advisory Health Council instead of the Advisory Council of the Institute of Allergy and Infectious Diseases.

PLANS

The most recent grant was to Louisiana State University in June 1961. Following this, a study was initiated to review the progress of each of the centers. After a preliminary appraisal, it was decided to limit the number of centers to six in 1962 in order to allow more time for the evaluation of these administratively complex operations. Furthermore, NIH wished to accumulate more data in order to determine the optimum balance between our investment in these centralized overseas units on the one hand, and our support of individual international projects on the other hand. Thus, in the latter part of fiscal year 1962 or early in fiscal year 1963 only one additional grant (to an American university for the development of a center in Africa) is planned.

In fiscal year 1963 no increase in support for the ICMRT program is being requested. The same amount ($3.19 million) which was allocated from the special international appropriation in fiscal year 1962 will provide adequate support for the continuation of the present five centers. In addition, these funds will permit the development of one new center and the appropriation will provide for modest strengthening of some of the present centers.

CHANGE IN RESPONSIBILITY FOR INTERNATIONAL CENTERS

Mr. **Fogarty.** The powers that be do not want you to operate this any more, do they?

Dr. **Andrews.** That is right. Due to the change in the origin of the funds for these international centers, it is no longer necessary to have one Institute represent the interests of all the others. So we are bowing gracefully out of the situation but we will retain an interest in them because of the role we have played in the development of this program.

Mr. **Fogarty.** What do you mean, "bowing out gracefully," as gracefully as you could under the circumstances? Is that what you mean?

Dr. **Shannon.** The primary objective is to permit these centers, over the years, to undertake work on many problems other than those that are the primary responsibility of this one Institute. As the centers develop they will have relationship to metabolism, nutrition, heart disease, cancer, and problems of the central nervous system. In a situation involving so many Institutes, we feel that it is better, in the long run, to administer them outside of the area of a single categorical institute. How this will be handled from the standpoint of council review will depend largely upon whether or not the Division of General Medical Sciences is in fact set up as a new institute.

Mr. **Fogarty.** It may turn out that this decision was wrong and it might be better if left in the Allergy Institute.

Dr. Shannon. If this turns out to be the case——

Mr. Fogarty. Before you shut Dr. Andrews off; Dr. Andrews, why don't you tell us now what you think?

Dr. Andrews. We are very happy to collaborate with the present scheme.

Mr. Fogarty. You cannot do much about it, can you? I thought you were doing a pretty good job with this. I felt you got off on the right foot.

Dr. Andrews. I am not aware that there have been any complaints about it, but I think that the proposed shift in coordination can provide better leadership in this complex field of international research and training than we would be able to do.

Dr. Shannon. This is not a recent decision. Right from the beginning it was envisaged that this would eventually take place but in establishing, particularly oversea units——

Mr. Fogarty. You did not tell anybody about it.

Dr. Shannon. I believe we told this committee, sir.

Mr. Fogarty. You did?

Dr. Shannon. Originally the funds that financed this appeared in six institutes. We brought them together in one institute for the purposes of administration with the intent, at a later time, to place it in the general appropriation rather than the categorical appropriation.

VIRUS RESEARCH

Mr. Fogarty. All right, Doctor, you do a lot of work in the virus field. What is a virus?

Dr. Andrews. A virus is a very small particle of ribonucleic acids and a protein, which cause disease. These are small enough to go through such filters as porcelaneous filters, under pressure.

Mr. Fogarty. Is it alive?

Dr. Andrews. It is capable of reproduction, and by that definition it is alive. It is capable of replication in cells and of destroying these cells so that by the destruction it causes disease.

VIRUS-FREE ANIMALS

Mr. Fogarty. Can an animal live without a virus?

Dr. Andrews. Yes.

Mr. Fogarty. Can you grow virus-free animals?

Dr. Andrews. Yes; we have virus-free animals, along with germ-free animals.

Mr. Fogarty. Are they just as difficult to grow as a germ-free animal?

Dr. Andrews. Even more so, if anything. It is much easier to get rid of bacteria than it is viruses.

Mr. Fogarty. Who is doing this work?

Dr. Andrews. In our own Institute, we provide facilities for a number of the other Institutes, using germ-free animals or doing germ-free studies. We have some of our own going on as well. I am sure it is an advantage to all to have these concentrated in one particular area.

Mr. Fogarty. You do not have many, do you?

Dr. Andrews. There are three other germ-free centers in the world.

Mr. Fogarty. You do not have many virus-free animals, do you?

Dr. Andrews. I think there is a considerable number. I can supply it for you, but it has not occurred to me but what there would be a good many. We have hundreds of virus-free mice.

Dr. Shannon. They are measured in the hundreds rather than the thousands.

Mr. Fogarty. That is fairly few, is it not?

Dr. Andrews. The thing which limits the number of germ-free guinea pigs is that they all have to be delivered by cesarean section. So far no one managed to my knowledge at least, of being able to reproduce a line naturally.

Dr. Shannon. They have, with mice.

EQUIPMENT FOR RAISING GERM-FREE ANIMALS

Mr. Fogarty. I went through the laboratory at Notre Dame and saw them raising some of these in these huge cylinder houses. That was some years ago. I assume in your Institute you have more up-to-date equipment.

Dr. Shannon. Actually, the basic equipment we use is that developed at Notre Dame. There have been many advances in equipment such as using plastics instead of steel for short-term experiments but the longer term experiments it still seems that the original equipment is quite good.

There are three large centers, and I do not consider NIH a large center. There is the one at Notre Dame, one Dr. Reyniers has set up at Tampa, Fla., and one in Sweden which we support quite broadly.

Mr. Fogarty. They were doing some of this work at Walter Reed Hospital, were they not?

Dr. Shannon. Yes, sir. There is a great deal of cooperation between NIH and Walter Reed.

Mr. Fogarty. Walter Reed is not really called a center.

Dr. Shannon. No, sir.

Mr. Chairman, I think in the coming year or two this technique will have been in use long enough and in sufficiently broad programs for us to re-evaluate it. It is our belief that with the next 3, 4, or 5 years, there should be a concerted effort to make this tool much more freely available to biological investigators.

Mr. Fogarty. The last time I checked into it there weren't enough animals to go around.

Dr. Shannon. This is still the case, sir.

TRANSPORTING GERM-FREE ANIMALS

Mr. Fogarty. We were having difficulty building something in which you could transport these animals.

Dr. Shannon. I think Dr. Reyniers has licked that problem within the past 2 years.

It is still very costly to transport them, but it is now possible to do so. This illustrates the need to expand the germ-free animal resources so that adequate numbers are produced for a number of investigators.

VIRUS-FREE ANIMALS

Mr. FOGARTY. This virus-free animal is something new to me, Doctor. I have heard about the germ-free animals for some time. I am surprised to hear that you have hundreds of virus-free animals.

Dr. SHANNON. The problem with the virus-free animal is that you never know whether an animal is virus-free until you have tested it for every known virus.

Mr. FOGARTY. What is a virus-free animal?

Dr. SHANNON. A virus-free animal is an animal you have not found a virus in—yet. That is about it.

Quite frankly, sir, the viruses are not all we test for in a germ-free animal. The only study that has been made is to test germ-free animals for the more conventional viruses that are commonly found in laboratory animals. These are not present in any of the germ-free colonies.

Mr. FOGARTY. Do you have one virus-free animal, according to your definition?

Dr. SHANNON. According to my definition, there are no animals that either Dr. Andrews or I could say with certainty do not possess any virus—all we know is that they do not possess the ones that have been looked for. Finding a bacteriological contamination is simpler than finding a virus which requires highly specialized tissue culture techniques, et cetera. It is much more difficult to be certain that viruses in general are not present than that bacteria in general are not present.

Mr. FOGARTY. Mr. Denton?

ALLERGY DEFINED

Mr. DENTON. Just what is an allergy?

Dr. ANDREWS. An allergy is a response to a particular substance in a small quantity or in a small number of the population. This differs from a primary intoxicant or irritant because it is not uniformly harmful to most people. It harms only a very few.

Mr. DENTON. You mean it is some substance that harms just a few people?

Dr. ANDREWS. That is right.

Mr. DENTON. Is it caused by a germ or a virus?

Dr. ANDREWS. A number of substances, both organic and inorganic, can cause allergies or cause these hypersensitivities.

Mr. DENTON. I do not quite understand. Is it caused by a germ?

Dr. ANDREWS. No.

Mr. DENTON. Could it be caused by a germ?

Dr. ANDREWS. It can be caused by the chemical content of germs, yes; and sometimes it is.

Mr. DENTON. Can it be caused by a virus?

Dr. ANDREWS. I am not aware of any such instances.

Mr. DENTON. Why do you have infectious diseases and allergies together in the same Institute? Why do you combine infectious diseases and allergies in the same grouping?

Dr. SHANNON. Mr. Denton, the reaction of the body to the products of infection and the reaction of the body to a host of protein-like chemical substances or carbohydrates that produce the characteristics of infection, have much in common. In other words, the underlying reaction of the body in allergy is the same as the underlying reaction of the body in developing immunity to disease.

Mr. DENTON. Is hay fever caused by allergy?

Dr. SHANNON. Hay fever is caused by allergy. The most typical example is the protein contained in pollen.

Mr. DENTON. That is goldenrod, for example.

Dr. SHANNON. Precisely.

Mr. DENTON. It causes some people to have——

Dr. SHANNON. Symptoms of disease.

Mr. DENTON. Yes.

Dr. SHANNON. This is due to a protein material that comes from outside. This disease is not too different from the type of disease symptom caused by the release of comparable materials growing in the body.

CAUSE OF INFECTIOUS DISEASE

Dr. DENTON. Infectious diseases are caused by some type of living germ or virus.

Dr. SHANNON. If one takes an extract of a bacillus and injects that under the skin, one can reproduce—and this has been done particularly well in the last few years—all the characteristic symptoms of, say, typhoid fever including many of the underlying tissue changes. To produce the symptoms of disease does not require the presence of living organisms in the body but it does require certain highly specific products derived from those organisms.

In allergies in general, the pollen allergies, the symptoms of disease are caused by certain of these products that have the ability to produce abnormal symptoms. The reactions of the body for handling externally derived materials are much the same whether those materials are inhaled or are derived from infection.

IMMUNIZING FOR ALLERGIES

Mr. DENTON. You can get a serum injection which will prevent or at least kill germs or viruses. Can you do that with an allergy?

Dr. SHANNON. The answer to that is "No." In the case of dyphtheria, for example, the symptoms of the disease are due to the release of a toxin which has a specific effect on tissue. You can take this toxin, inject it into animals, and produce an antitoxin, that is, a material which combines with and, in effect, neutralizes the toxin.

You cannot do precisely the same thing with the so-called allergy. However, you can inject minute doses of an allergen to build up the ability of the body to combine with it and thus remove it from the system. In this sense they are also comparable.

Mr. DENTON. There is no antidote to hay fever, is there?

Dr. SHANNON. You can immunize and develop a tolerance for or capability of handling the allergen so that with the inhalation of the pollen there will be no allergic manifestations. But there is no antiserum that can be injected once the allergy is established with the subsequent disappearance of the——

COMMON COLD PREVENTION

Mr. **Denton.** Do you have a serum to prevent the common cold?

Dr. **Andrews.** Not at present. This is one of the principal programs we intend to stage this year.

Mr. **Denton.** Some years ago doctors used to inoculate people with cold serum to prevent their getting colds. A doctor told me some years ago that was not possible. They can inoculate you for flu but there was nothing to prevent a cold.

What is the history of that?

Dr. **Andrews.** There is a number of trade vaccines available in the market. Some of these are well devised and some are not.

There are two which we recognize as being bona fide, good vaccines. One is against influenza and the other is against adenoviruses.

This is one of the causes of the common colds.

Dr. **Shannon.** It is a very complicated thing. About 45 to 50 transmittable agents have been isolated, any one of which can produce the symptoms of the common cold. In other words, the common cold is caused by a number of different agents.

The important thing in the adenoviruses that Dr. Andrews just mentioned is this: one of those viruses is the causative agent of somewhere between 40 and 60 percent of all upper respiratory diseases in children in the 3 to 5 age group. A vaccine is being developed that may prevent this segment of the infections which together make up the common cold. However, it will not affect other large areas. The common cold is not due to a single thing but due to multiple things. To prevent the common cold we should have to provide an immunizing agent for each of the causes. This is now obviously impossible.

Mr. **Denton.** I take it the reason you cannot get a serum is because there are too many viruses and germs?

Dr. **Shannon.** That is right.

Mr. **Denton.** For influenza you can buy different types.

Dr. **Shannon.** There are only two major types which cause influenza and these vary somewhat in what is called——

Mr. **Denton.** You mean A and B?

Dr. **Shannon.** That is right. These vary from year to year in their characteristics but it is possible to keep up with them by changing the type of vaccine on a year to year basis. There are only two basic classes of influenza virus, whereas in other respiratory diseases there are somewhere between 40 and 60.

ECONOMIC EFFECT OF COMMON COLDS

Mr. **Denton.** I heard somewhere the common cold causes more lost time than any other disease.

Dr. **Shannon.** This is a well-documented statement, particularly when applied to industrial absenteeism or school absenteeism.

Mr. **Denton.** Do you think there is a possibility of getting an antidote to it?

Dr. **Shannon.** Eventually, not to completely irradicate the common cold but against those agents, and hopefully there will be only three or four,which are the predominant cause of most common colds.

EFFECTIVENESS OF COLD SERUMS

Mr. DENTON. What happened to the serum they used to give you for colds?

Dr. SHANNON. That wasn't very good.

Mr. DENTON. It was not effective?

Dr. SHANNON. That is right. Different agents hit different age groups. The Army currently is using one for one of the adenoviruses that causes what they call recruit fever. This is an upper respiratory disease which affected 70 to 80 percent of the recruits during the first 6 to 8 weeks of their residence in a camp. Again this is different from the other adenovirus which hits youngsters in the 3- to 5-year-old age group.

What will eventually happen is that there will be three, four or five, vaccines for specific virus groups. There perhaps never will be one vaccine for the common cold.

Mr. DENTON. That is all.

CORRELATION OF RESEARCH WITH OTHER DEPARTMENT

Mr. MARSHALL. You are acquainted with the laboratory that the Department of Agriculture has at Ames?

Dr. ANDREWS. I know of it; yes sir.

Mr. MARSHALL. Are you correlating your work with the work of that laboratory?

Dr. ANDREWS. There has been a joint effort in at least the para-influenza viruses which are common to cattle and to man, so that to this degree there has been some correlation.

Most of the interest, however, has to do with domestic animals on one hand and man on the other.

Mr. MARSHALL. How do you coordinate your work here with the similar work done there?

Dr. ANDREWS. We try to keep abreast of what is happening in the Department of Agriculture in this area by correspondence with the individuals who are concerned with it, and I think they try to do the same thing.

When this laboratory was located more or less locally it was somewhat easier than it is at present, but we still manage to maintain correspondence relationships at least.

Mr. MARSHALL. Have you been finding you get good cooperation from them?

Dr. ANDREWS. Yes, sir.

Mr. MARSHALL. That is all, Mr. Chairman.

Mr. MICHEL. I have no questions.

Mr. FOGARTY. Is there anything else you wish to say, Doctor?

Dr. ANDREWS. Nothing, sir.

Mr. FOGARTY. Thank you very much.

(The following was submitted for the record at the request of the committee.)

Deaths, Disability, and Cost of Allergy and Infectious Disease

Department of Health, Education, and Welfare, Public Health Service

NATIONAL INSTITUTES OF ALLERGY AND INFECTIOUS DISEASES

Statistics of the annual number of deaths and total current number of reported illnesses caused by selected diseases dealt with in the National Institute of Allergy and Infectious Diseases, and the estimated annual cost to the Nation are presented in table I.

Death attributable to allergic, infectious, and parasitic diseases during 1959 are used since National Office of Vital Statistics advises only preliminary data are available for 1960. Since most of these conditions cause illness rather than death, morbidity is presented for 1960 to reflect the extent of impairment created by these diseases. The following table illustrates the above and reports only those deaths and cases which are diagnosed by a reporting laboratory or a qualified physician, health officer, or other professional person.

Table I

Category	Reported deaths 1959 [1]	Reported cases, 1960
Allergic diseases:		
Asthma	4,984	----------
Other allergic disorders	92	----------
Infectious and parasitic diseases:		
Bacterial diseases:		
Scarlet fever and streptococcal sore throat	130	315,173
Septicemia and pyemia	1,760	----------
Tuberculosis	11,456	55,494
Venereal diseases	3,106	383,747
Viral diseases:		
Acute upper respiratory infections (includes common cold)	971	----------
Influenza	2,845	258,062
Hepatitis	897	41,666
Measles	385	441,703
Poliomyelitis, acute	454	3,190
Unspecified bacterial and viral disesaes:		
Bronchitis	3,840	----------
Dysentery, all types	[2] 278	[3] 12,487
Meningitis, all types	2,907	5,983
Pneumonia, all types	52,194	[4] 8,090
Infections of the kidneys	6,822	----------
Infections of the newborn	5,062	----------
Infections of the skin	632	----------
Other bacterial and viral diseases	3,712	[4] 448,861
Fungal diseases: all types	336	----------
Parasitic diseases:		
Amebiasis and other protozoal diseases	124	[5] 3,424
Hookworm and other worm diseases	65	[6] 12,161
Total reported	103,052	1,990,041

[1] Reported deaths, all causes, totaled 1,656,814 in 1959.
[2] Does not include 7,400 deaths ascribed to gastroenteritis and colitis.
[3] Includes shigellosis only.
[4] Incomplete reporting. Only certain States and/or cities require reporting of this item.
[5] Only amebiasis reported.
[6] Only hookworm reported.

Data regarding certain specific diseases of interest to the National Institute of Allergy and Infectious Diseases are not available. Of particular interest in this connection are stapyhylococcal infections, which are distributed among several of the entries in attached table, particularly "septicemia and pyemia," "infections of the kidney," "infections of the newborn," and "infections of the skin."

Table II presents estimates of the incidence (number of cases per year) associated disability, and cost to the Nation for the allergic, infectious, and parasitic diseases. Figures for the annual cost to the Nation include only the value of time lost from work due to disability. Statistics are not available to include the cost of medical and hospital care, drugs, and compensation specifically attributable to these diseases. Table II attached.

TABLE 2.—*Allergic, infectious, and parasitic diseases—Number of cases, associated disability, and cost to the Nation for the period July 1, 1958, to June 30, 1959 (unless otherwise noted)*

[Data (unless otherwise noted) from various issues of the series "Health Statistics From the U.S. National Health Survey," National Center for Health Statistics, Public Health Service]

	Number of cases	Restricted activity (days)	Bed disability (days)	Work loss (days)	School loss (days)	Average daily number of persons with restricted activity	Annual cost to the Nation [1]
Upper respiratory conditions: Common cold, sinusitis, pharyngitis, tonsillitis, laryngitis, tracheitis	142, 381, 000	393, 722, 000	156, 109, 000	39, 461, 000	64, 284, 000	1, 078, 690	$685, 674, 000
Other respiratory conditions: Influenza, pneumonia, bronchitis (acute), pneumoconiasis, emphysema	72, 966, 000	306, 349, 000	169, 915, 000	39, 777, 000	46, 390, 000	839, 312	691, 165, 000
Other infectious and parasitic diseases:							
Acute conditions	44, 240, 000	203, 719, 000	90, 770, 000	17, 841, 000	49, 255, 000	558, 134	310, 005, 000
Chronic conditions (includes tubersulosis) [2]		33, 300, 000	16, 000, 000	4, 600, 000	800, 000	91, 233	79, 930, 000
Allergic diseases:							
Asthma and hay fever		[2] 96, 553, 000	[2] 30, 022, 000	[3] 31, 000, 000		[2] 264, 529	[3] 538, 656, 000
Other allergic disorders		[3] 28, 560, 000		[3] 11, 000, 000		[3] 78, 247	[3] 191, 136, 000
Total	259, 587, 000	1, 062, 203, 000	462, 816, 000	143, 679, 000	160, 729, 000	2, 910, 145	2, 496, 566, 000

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[1] Includes only value of time lost from work, calculated on the Department of Commerce estimate of $4,344 average annual earning per full-time equivalent employee, and on a 40-hour workweek, 50 weeks per year.

[2] For the period July 1, 1957, to June 30, 1958. More recent data not yet published.

[3] Nachtigall, H. B., "Compensatory Medicine," 9:5, 1957; and "Health in California," Department of Public Health, State of California, 1957. Both reflect surveys made before 1957. More recent data are not available.

Highlights of Research Progress in Allergy and Infectious Diseases, 1961

VIRUS DISEASES

Eaton agent linked to atypical pneumonia

The etiology of nonbacterial pneumonia has been a subject of considerable controversy among microbiologists for the past 20 years. Much interest has centered about the agent (taxonomic status still undetermined) recovered by Dr. Monroe D. Eaton and his colleagues in 1944 from patients with atypical pneumonia. A cooperative epidemiologic investigation, completed recently by Dr. Robert M. Chanock of the National Institute of Allergy and Infectious Diseases and a group of naval scientists, among recruits at the Parris Island Marine Training Center, offers the most complete evidence to date associating the Eaton agent with atypical pneumonia. The report appears in the Journal of the American Medical Association.

Over a 6-month period the investigators detected Eaton agent infection in 161 of 238 (68 percent) patients with atypical pneumonia. The scientists were able to recover the agent from 14 of 17 pneumonia patients who developed fluorescent stainable antibody during convalescence. Infection as revealed by serologic techniques occurred at a significantly lower rate (6 percent) among patients without respiratory illness, thus diminishing the possibility of a fortuitous association of the agent with disease.

The conditions at Parris Island during the study interval provided the scientists an unusual opportunity to investigate the ecology of Eaton agent infection as measured by antibody titer. Activity of influenza and adenoviruses was limited, while the incidence of Eaton virus was high, with 44 of every 100 recruits infected during the 3-month training interval. For those without detectable Eaton antibody on entering the service, the risk of infection was 53 percent. The risk of developing an Eaton-positive pneumonia was also high—1.5 percent. From these data, it would appear that 1 in 30 infections resulted in a clinically apparent pneumonia. Although Eaton infection was also associated with febrile respiratory illness in which pneumonia was not evident, the majority of infections appeared to be asymptomatic.

Although infection with this agent is not rapidly transmitted as is influenza, the Eaton agent was found to be widely disseminated throughout the camp. In certain of the platoons it remained for at least 8 to 9 weeks as evidenced by the occurrence of serologically positive pneumonia. The scientists concluded that the combined attributes of poor spreading ability, together with a long incubation period, are ideally suited to maintain such an agent for a long interval in an ever-changing recruit population.

Type A–16 Coxsackie virus causes distinctive illness

As a result of a recent epidemiologic study in California, it appears reasonable to add the syndrome of vesicular stomatitis and exanthem to the clinical manifestations associated with infection by various immunologic types of Coxsackie virus.

Dr. Magoffin and his associates at the California State Department of Public Health report on this study in the Journal of the American Medical Association. The work was supported by a grant from the National Institute of Allergy and Infectious Diseases.

For a number of years herpangina has been recognized as a widely prevalent childhood disease with distinctive clinical manifestations caused by some six types (2, 4, 5, 6, 8, 10) of group A Coxsackie viruses. In 1957, an outbreak of illness, similar to herpangina but differing in several significant aspects, occurred in Toronto, Canada, and was linked to Coxsackie virus, type A–16. It remained unique until 1959 when an apparently identical syndrome was observed for the first time in various localities in California.

By September the syndrome had been observed in all the major geographic areas of the State and an estimate of total incidence running into the thousands had been made by the State department of health. Medical histories of 33 cases from 18 households were taken. From 15 of these patients the investigators obtained specimens for viral laboratory studies.

In its typical form the illness was mild, occurred during the summer, predominantly in children from 1 to 10 years of age, and was highly contagious to other youngsters in the household. The Toronto outbreak was characterized by fever, discrete vesiculo-ulcerative lesions of the pharynx and mouth, and a maculopapular exanthem which often progressed to a vesicular eruption on the hands and feet. The syndrome in California generally conformed to a description of the Canadian cases. In each outbreak, the clinical manifestations were distinguishable from herpangina by the frequent presence of lesions on the buccal mucosa and tongue and in eight cases by the occurrence of a maculovesicular exanthem. Of the 15 cases whose stools were tested, 10 yielded Coxsackie virus, type A–16. One additional child whose stool did not yield the virus had a high neutralizing antibody index.

The illness is not known to have been recorded previously in the United States. According to the investigators, the experience with Coxsackie A–16 provides a notable example, in the brief history of entero-virus infections, of the sudden emergence of one virus type, in an outcropping of clinical illness in one geographic area, followed by a return to obscurity for a variable time before unpredictably reappearing in some distant locality.

Eaton agent pneumonia treated with antibiotic

Results of the study are summarized in the April 15 issue of the Journal of the American Medical Association. The authors are Dr. J. R. Kingston, Dr. M. A. Mufson, L. P. Hellman, Dr. M. A. Manko, Dr. J. Boyers of the Department of Navy, Bureau of Medicine and Surgery; and Dr. R. M. Chanock, W. D. James, and H. H. Fox of the National Institute of Allergy and Infectious Diseases, National Institutes of Health.

The group conducted a controlled, double-blind study on 290 Marine recruits with nonbacteriologic pneumonia to evaluate the efficacy of demethylchlortetracycline on primary atypical pneumonia associated with the Eaton agent. This agent (taxonomic status still undetermined) was first recovered in 1944 by Dr. Monroe D. Eaton and his colleagues from patients with atypical pneumonia. The antibiotic was developed by scientists at Lederle Laboratories.

Of the 290 patients, Eaton agent pneumonia was diagnosed in 109. The scientists administered demethylchlortetracycline to approximately half of the Eaton-positive patients daily for 6 days and the remainder were given a placebo. In the treated group, symptoms such as fevor, cough, rales, and malaise vanished and lung infiltration cleared far more rapidly than in the control group. Furthermore, fever did not return after the termination of treatment, although some 40 percent of the untreated cases were still febrile at that time. These latter results—lung clearance plus permanently banished symptoms—suggest direct drug action on the disease process itself rather than the mere antipyretic effect contended by others.

Among 35 patients whose illness was associated with known respiratory viruses other than Eaton, antibiotic administration had little effect. In 122 patients with unidentifiable pneumonia, symptom duration was reduced. However, the chemotherapeutic effect was found to be significantly less, statistically speaking, in this group than in the Eaton-positive group.

Neutralization test diagnostic aid in virus infection

Although rapid antibody response often renders neutralization tests of doubtful value in diagnosing many viral infections, results of a large-scale study by grantees of the National Institute of Allergy and Infectious Diseases have now demonstrated considerable merit in the recently developed colorimetric (metabolic inhibition) procedure for assaying neutralizing antibodies to types 1–5 Coxsackie group B viruses.

The neutralizing antibody response appears to be highly type-specific in the initial infections with any of these 5 types of group B virus. However, heterotypic responses occur more often in later infections arising from the booster effect of the current virus on the antibody levels of previous infections with other virus types.

According to the authors, the new test should become a valuable adjunct to virus isolation for diagnosing this group of infections. They add that in this particular study, at any rate, it is superior to the poliomyelitis neutralization test, which is usually found positive in 40 percent of the cases with viral isolations.

Authors of the report, which may be found in the Journal of Immunology, are Drs. Edwin H. Lennette, Tak T. Shinomoto, Nathalie J. Schmidt, and Robert L. Magoffin from the Viral and Rickettsial Disease Laboratory, California State department of public health.

New virus (respiratory syncytial) linked to infant pneumonia

The etiologic association of respiratory syncytial virus (RS) with respiratory tract illness in infants and children has been confirmed by studies supported or conducted by the National Institute of Allergy and Infectious Diseases. The four studies, conducted at Children's Hospital, D.C., and NIAID's laboratory of infectious diseases and laboratory of clinical investigation were reported in the Journal of the American Medical Association.

From March through July 1960, 56 strains of respiratory syncytial virus were isolated from 346 infants and children treated with respiratory illness at Children's Hospital. Only 4 strains were recovered from 272 control subjects without such illness. The virus was isolated most frequently from infants less than 7 months of age who had bronchiolitis or pneumonia. RS virus was recovered from 42 percent of all patients with bronchiolitis and from 24 percent of all patients with pneumonia during the study period, while only 1 percent of control patients yielded the agent. Virus was also recovered from 12 percent of infants and children with febrile respiratory illness which was not severe enough to require hospitalization. Dr. Robert M. Chanock is senior author of the report.

During a 3-year period at the same hospital, a second study by Dr. Robert H. Parrott of the Children's Hospital and his associates obtained serologic evidence of RS virus infection in 11 percent of 1,038 infants and children confined with pneumonia, bronchiolitis, croup, or pharyngitis with bronchitis. This rate of infection was 5.5 times greater than that among control patients free of respiratory tract symptoms. When serologic findings were adjusted for the known sensitivity of the complement-fixation technique used, it was estimated that 21 percent of the children with respiratory tract illness were infected with RS virus. Virus-infection illness association was more striking among infants than older children and particularly among patients with bronchiolitis (estimated 36 percent) or bronchopneumonia (estimated 21 percent).

The time pattern of the infections also suggested that RS virus infection may be present during certain months of every year and at times is responsible for a large segment of severe and often fatal respiratory tract illness in children. The authors state that effective immunization against this agent in early infancy could prevent much of this type of illness.

A third report by Dr. Howard M. Kravetz, of NIAID's Laboratory of Clinical Investigation, and associates describes results of tests involving adult male volunteers. Nasopharyngeal inoculation with RS virus was followed by a common cold-like syndrome lasting about 5 days in 20 of 41 volunteers. Virus was recovered from 85 percent of those who became ill and from 62 percent of those who did not. The observed illness was milder than that associated with RS virus infection in children, and it is suggested that this represented a protective effect resulting from previous infection.

A fourth report by Dr. Karl M. Johnson, Laboratory of Infectious Diseases, NIAID, and associates adds data obtained from the same adult volunteers. Administration of RS virus resulted in infection in 33, and mild upper respiratory illness in 20, of 41 of the subjects. The observed association between virus challenge and subsequent illness was strengthened by the finding that illness never preceded initial RS virus isolation and the fact that illness occurred for the most part in individuals who shed detectable virus for an interval of more than 2 days. All cases represented reinfection as all volunteers had detectable RS neutralizing antibody prior to challenge.

The journal, in a separate editorial, points out that with these studies as much as 60 percent of children's severe respiratory illnesses may be explained. The NIAID-Children's Hospital study group 2 years ago established the parainfluenza viruses as an important cause of respiratory disease in the young. Another recent study suggested that the Eaton agent was associated with lower respiratory tract illness. Together, the RS virus, Eaton agent, parainfluenza, as well as the influenza and adenoviruses, represent the 60-percent figure and suggest the need of vaccine development.

New virus of mice isolated and described

The recovery of a new mouse virus by National Institute of Allergy and infectious Diseases scientists is reported in the Journal of Experimental Medicine. The Institute investigators are Dr. Wallace P. Rowe and Worth I. Capps.

The agent induces a nonfatal disease in infant mice, characterized by acute massive necrosis in the medulla and cortex of the thymus gland, granulomatus reaction, and subsequent restoration of essentially normal structure with scarring. Intranuclear inclusion bodies are produced in thymocytes in the early stage of the infection.

The initial isolation of the thymic agent was encountered as an incidental finding in General Purpose strain mice during a blind passage series for another agent. Since that series the thymic agent has been carried through 39 serial newborn mouse passages with induction of macroscopic thymic necrosis in 744 (96 percent) of 807 passage mice examined at 6 to 8 days, and in 72 of 75 examined at 14 to 20 days.

Evidence for the viral nature of the agent is its ability to pass through bacteria-tight filters, inability to grow on bacteriologic media, resistance to antibiotics, and the presence of nuclear and cytoplasmic karyonnular particles in electron micographs of acutely infected thymuses. Also, the production of intranuclear inclusion bodies is strongly indicative of a virus.

The type of disease and of inclusion body, host range, and ether sensitivity of the thymic agent serve effectively to indicate its distinctness from other known mouse viruses. Thymuses of infant mice inoculated with polyoma virus, mouse salivary gland virus, K virus, mouse adenovirus, and mouse strains of reoviruses types 2 and 3 have been examined grossly and microscopically. In no instance have similar lesions been seen. Serologic comparison also indicated the distinctiveness of the virus.

Isolation of Ilheus encephalitis virus in Panama

The first strain of Ilheus virus isolated from mosquitoes in the Republic of Panama and two recoveries of the virus from birds are described in separate reports by Drs. Enid de Rodaniche and Pedro Galindo in the American Journal of Tropical Medicine and Hygiene.

The extent to which Ilheus virus may be implicated in human encephalitides is unknown but the agent is antigenically related to the West Nile, St. Louis, and Japanese B groups which cause human illnesses. In tests of specimens taken from 195 residents of Panama's Darien Province, 43.7 percent of the sera gave a positive reaction against Ilheus, a surprisingly high percentage considering that Ilheus encephalitis has not been recognized clinically in Panama.

The isolates in mosquitoes came from pools of two different species. The 2 recoveries of the virus from birds were made from more than 40 different species.

The significance of birds in the ecology of a number of arthropod-borne viruses is being recognized increasingly. In the study reported here, 48 sera from birds captured in Darien, and 118 sera from birds of Bocas del Toro, Panama, were tested. These came from more than 40 different avian species and from them 2 recoveries of Ilheus encephalitis were made, 1 from a little blue heron and 1 from a toucan. No other virus was obtained from birds in Bomas del Toro but two strains of an as yet unidentified virus were isolated in the Darien birds.

Ilheus virus was known to be present in mosquitoes in Darien shortly prior to the capture of the birds tested. Five of 62 birds from Bocas del Toro and 2 of 68 birds from Darien had neutralizing antibodies against this virus in their blood.

This isolation of Ilheus virus from birds is the first in Central America. Further studies are needed to assess the relative importance of the heron and toucan, as well as other birds, in the ecology of this infection in Panama.

Respiratory syncytial virus implicated in epidemic

An epidemic of acute respiratory disease at Harbor General Hospital in Los Angeles was probably caused by respiratory syncytial (RS) virus, an agent recently reported on by scientists of the National Institute of Allergy and Infectious Diseases and Children's Hospital, Washington, D.C. The study was supported in part by the National Institute of Allergy and Infectious Diseases. The authors are Drs. John M. Adams, David T. Imagawa and Kenneth Zike of the University of California School of Medicine. Their findings appear in the Journal of the American Medical Association.

During the epidemic a viral agent was isolated in HeLa and monkey kidney cells directly from throat washings. Cytopathic changes included syncytium (a multinucleate mass of protoplasm produced by the merging of cells), with giant cell formation and distinctive inclusion bodies. These changes compared closely to those recently described by NIAID's Dr. Robert M. Chanock and coworkers. Dr. Chanock named the agent "respiratory syncytial (RS) virus" because of the characteristic syncytium it produces in tissue culture.

The epidemic was characterized by a predilection for young infants, and by low-grade fever, cough, difficult and labored breathing, and cyanosis, with signs of bronchiolar obstruction and pneumonitis. The symptoms in older individuals were mild: sneezing, cough, hoarseness and thick, profuse nasal discharge. These findings are similar to those from a recent series of NIAID studies involving young children and adult prisoner volunteers.

The problem of finally establishing the agent of the epidemic as RS virus is being pursued in the laboratory. So far, all tests point to RS. Influenza and parainfluenza have been virtually ruled out; they are not readily isolated in HeLa cells, and fail to produce the characteristic cytopathic changes. These cytopathic changes have been neutralized by known RS antibody and by convalescent sera from several of the patients from whom the primary isolations were made.

New virus, Haden, found in calves

A new virus has been recovered from the gastrointestinal tract of normal calves. Possessed of a unique grouping of biological qualities, this virus has been named Haden (hemadsorbing, enteric) by its discoverer, Dr. F. R. Abinanti. A description appears in "Virology" in a report by Dr. Abinanti and Mildred Warfield of the Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases.

The most distinguishing characteristic of the virus is its pattern of hemadsorption. Erythrocytes adhere to the cell sheet in aggregates that vary from a few cells to large clumps. This is in marked contrast to adsorption with myxoviruses where individual cells are diffusely adsorbed over an entire cell sheet.

Six recoveries of the virus were made in 3-week- to 4-month-old calves from three widely separated farms. Approximately 86 percent of the adult cattle in the tested herds had hemagglutination inhibition titers of 1:20 or greater. High levels of HI and neutralizing antibodies developed in the calves following recovery of the virus, and when virus was given by aerosol, calves also developed high antibody levels but no obvious clinical signs of disease.

Scientists visit Moscow on exchange mission

Drs. Robert J. Huebner, Alexis Shelokov, and Robert M. Chanock of the National Institute of Allergy and Infectious Diseases recently returned from the 1961 infectious diseases and microbiological exchange mission to the U.S.S.R. Accompanied by three other mission members, Dr. William McD. Hammon of the University of Pittsburgh, Dr. Fred M. Davenport of the University of Michigan, and Dr. Edwin H. Lennet of the California State Department of Health, the group visited medical research centers in Moscow, Leningrad, Kiev, and peripheral laboratories in Uzbekistan and Georgia.

Insights into Soviet medical science gained from their mission were reported to more than 200 colleagues at a National Institute of Allergy and Infectious Diseases seminar.

A summary of their report indicates—

> Goal-oriented Soviet medical science has a "terrific sense of competition" with the rest of the world and is quick to convert its early research successes to practical application;
>
> The average Soviet scientist feels he has sufficient freedom in pursuing his studies within the framework of public health goals set by senior scientists of the Academy of Medical Sciences in Moscow. Soviet scientists wonder how the United States achieves medical successes without similar planned goals and deadlines, although they recognize the leadership of the United States in fields such as virology, in which their own programs are only about 5 years old. The Soviets continue to depend on other nations for data stemming from basic research in the biological sciences;

The Soviets have strong interests in preventive medicine and are vigorously pursuing vaccine development programs. They are utilizing an oral polio vaccine they produced from "seed" virus supplied from Dr. Albert Sabin of the University of Cincinnati. A billion doses of this vaccine are now being prepared, some of which the Soviets will offer to other countries. They have given extensive trial to a live-virus influenza vaccine, which they admit has drawbacks for application to pediatric medicine because of fever-producing reactions. Similar reactions also have been encountered with adenovirus vaccine for respiratory infections. A live-virus mumps vaccine has been given to 50,000 children by injection and appears to develop a good antibody response.

Further exchange visits by Soviet and American scientists in the field of infectious diseases are planned for the future.

California encephalitis virus found in snowshoe hare

Scientists from the Rocky Mountain Laboratory of the National Institute of Allergy and Infectious Diseases have made what is probably the first direct isolation of California encephalitis virus from a naturally infected vertebrate. The work by Dr. Willy Burgdorfer, Verne F. Newhouse, and Dr. Leo A. Thomas is reported in the American Journal of Hygiene.

The viral agent was isolated from the blood of a snowshoe hare captured in the Bitterroot Valley of western Montana and was identified serologically by animal susceptibility tests as California encephalitis virus. In complement-fixation tests against immune sera of 35 viral agents, the isolate gave positive complement-fixation only in the homologous and California encephalitis virus systems. The behavior of the virus was also studied in tissue culture and embryonated chickens.

The finding adds weight to the presumption that the disease is maintained in nature in a cycle of mosquitoes, rabbits, and ground squirrels and possibly other vertebrates, including domestic animals. It also indicates that the distribution of the virus might not be as limited geographically as previously believed.

In Kern County, Calif., where the virus originally was isolated from two species of mosquitoes, inapparent infection in man has been shown to be quite common; clinical illness has also been linked to the agent.

Four new adenoviruses described

From more than 50 strains of adenoviruses isolated during a longitudinal study of the microbial experiences of children in Washington, D.C., four new adenovirus types have been identified and described by Drs. Leon Rosen and Joseph A. Bell of the Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, and Dr. Samuel Baron of the Division of Biologics Standards. Their report appears in the "Proceedings of the Society for Experimental Biology and Medicine."

After all untyped adenovirus isolates had been grouped into four serotypes by means of hemagglutination inhibition tests, one strain of each type was chosen as the prototype for further study.

Some of the children yielding isolates of the new serotypes had minor illnesses of a variety of types. However, minor illnesses were extremely prevalent in the study population and the data available were not sufficient to determine whether the newly recognized adenoviruses were etiologically associated with any of them.

After reviewing these and other data persented, the Adenovirus Committee of the NIAID recommended that these viruses be designated adenovirus types 25, 26, 27, and 28, respectively.

Parainfluenza virus capable of reinfecting adults

Myxovirus parainfluenza types 1, 2, and 3 have been isolated with increasing frequency in the United States, Canada, Denmark, England, and France. Epidemiologic studies have associated these viruses with respiratory illnesses of varying severity, including mild respiratory infections, acute croup, bronchiolitis and pneumonia in young children.

At present, little is known about the natural history of the infection of adults by these viruses. The authors of this study, Drs. H. H. Bloom and R. Jacobsen, of the Naval Medical Field Research Laboratory, Camp Lejeune, N.C., and Drs. K. M.Johnson and R. M. Chanock, of the National Institute of Allergy and Infectious Diseases, described the recovery of 15 strains of parainfluenza virus from adults. Their findings appear in the American Journal of Hygiene.

The study took place at Camp Lejeune, N.C., using individuals selected from Marine Corps units. The results strongly indicated that the adult infections represent reinfection, since neutralizing antibody was almost always detected in the acute phase serum. Parainfluenza virus was recovered from 15 patients, 11 with upper respiratory illness, 1 with parotitis, and 3 in the nonrespiratory control group (this was composed of individuals reporting with noninfectious ailments who had had no respiratory complaints within the preceding 10 days).

The investigators found that the infected adults shed a very small amount of virus compared with that shed by children. They experienced difficulty in re-isolating virus from frozen specimens and serodiagnostic methods proved relatively inefficient for this study. They suggest that the problems they encountered indicate that modification in technique may be necessary for the study of parainfluenza in this age group.

Caribbean island population naturally immune to polio

Recently poliomyelitis has appeared as an epidemic disease in the Caribbean. To use poliovaccine to best advantage it is esential that the local history of poliomyelitis be known. In the absence of epidemics, it is only from antibody surveys that a given population can be assessed to determine if it is ripe for an epidemic.

A serological survey of the Caribbean island St. Vincent, an area endemic for poliomyelitis, has been reported in the American Journal of Tropical Medicine and Hygiene. The study by Drs. R. Proctor, J. L. Melnick, L. Spence, and W. G. Downs, of Baylor University College of Medicine, Houston, Tex., and the Trinidad Regional Virus Laboratory, Port-of-Spain, Federation of the West Indies, was supported in part by a training grant from the National Institute of Allergy and Infectious Diseases.

Sera collected from 152 healthy young inhabitants born on St. Vincent were assayed for antibodies against all three types of poliovirus. None of those surveyed had ever been off the island. In spite of the fact that the island has never had an outbreak of poliomyelitis, a significant part of the population develops antibodies to each of the polioviruses by the age of 5 years. By young adulthood 86 to 95 percent of the population has antibodies against the disease.

The survey revealed that more than 90 percent of the young children of St. Vincent have developed measurable immunity to some type of poliomyelitis, and by the age of 20 everyone has done so. No samples were available from children under 2, so that the persistence of maternal autibodies was not assesed in this study.

The investigators speculate that as sanitary conditions improve in the islands, less spread of enterovirus will occur in early life under a blanket of maternal antibodies, with the result that the number of susceptibles will increase. As this shift occurs, vaccination programs become necessary to prevent epidemics. On St. Vincent the number of polio susceptibles is considerable in the young age group and may be expected to increase. Ideally, a program of vaccination in young children should be instituted and monitored by periodic antibody surveys, to insure that a high proportion of the population is maintaining its immunty.

Viruses cause 90 percent of lower respiratory infections

The cause of acute viral infections of the lower respiratory tract has been a matter of considerable speculation and is the subject of continuing studies by Dr. Alfred S. Evans, University of Wisconsin, a grantee of the National Institute of Allergy and Infectious Diseases. He and his colleague, Mary Brobst, report in the New England Journal of Medicine that between 90 and 95 percent of acute infections of the lungs and bronchi observed in 119 University of Wisconsin students were caused by viruses. The most impressive association they found was with the Eaton agent. Nearly 25 percent of the 119 students, hospitalized over a 7-year period, had infections associated with this agent.

The investigators note that their results are based on serologic responses and that questions have been raised in the past about the specificity of the Eaton agent antibody response because of the appearance of nonspecific substances like the cold agglutinins and other agglutinins in serums from many of the patients with viral pneumonitis. These doubts, they say, have been largely dispelled through the work of Dr. Robert M. Chanock and his associates of the National Institute of Allergy and Infectious Diseases, who have isolated Eaton agent directly from throat washings in such cases, and have shown the almost exclusive occurrence of Eaton-agent antibodies in patients with respiratory disease not associated with influenza, parainfluenza or adenovirus infections, and the absence of antibody rises in serums from patients without respiratory infections. The investigators report their serologic studies are in agreement with this.

Influenza, parainfluenza, and psittacosis viruses were also associated with acute infections of the lower respiratory tract in the study.

The investigators also suggest that the terminology of acute infections of the lower respiratory tract is confusing. The term "primary atypical pneumonia," widely used since World War II, they say, no longer seems appropriate because of recent demonstrations, including their own, of the diverse etiology of this syndrome. This is especially true since there is no reliable clinical feature or simple laboratory procedure that will differentiate one infection from another. A more useful classification could be based on the anatomic part involved (such as the lung or bronchus), the nature of the involvement, whether bacterial or viral, and the specific agent if known. Thus, such a term as viral pneumonitis or viral pneumonia due to Eaton agent or due to influenza might be substituted for "primary atypical pneumonia," the investigators conclude.

Coxsackie virus illnesses confused with polio

Dr. Robert L. Magoffin, of the California State Department of Public Health, reports that the occurrence of mild paresis associated with Coxsackie and other nonpoliovirus infections appears to have been an appreciable source of error in the clinical diagnosis of paralytic poliomyelitis in recent years in California.

In Pediatrics Dr. Magoffin and his associates describe 25 such cases, all of which were reported to the California State Department of Public Health as paralytic poliomyelitis during a recent 2-year period. The study was supported by a grant from the National Institute of Allergy and Infectious Diseases.

Paresis resulting from such infections, the investigators say, may be of little or no consequence in terms of residual disability; however, they stress that such cases are reported to the health officer as poliomyelitis and contribute to the official morbidity records utilized for determining local and national incidence rates of poliomyelitis.

As the widespread use of specific vaccines further suppresses the occurrence of involvement of the central nervous system in poliovirus infections, the authors believe it likely that these nonpoliomyelitis illnesses will comprise an increasing proportion of the cases of infectious paralytic disease coming to medical attention.

Coxsackie virus was recovered from all patients. Serologic studies in 16 of the patients revealed equivocal evidence of poliomyelitis in 2 cases, but in the remainder it appeared unlikely from the antibody pattern that poliovirus infection could have been associated with the present illness. There was no occurrence of paralytic poliomyelitis in members of the family of any of these patients, but in two families siblings of the patients experienced a milder febrile illness and also excreted the same type of Coxsackie virus as that recovered from the patients. The laboratory diagnosis of Coxsackie virus infection was further supported by significant antibody titer rises in 14 of 15 patients whose serums were tested. Serologic tests for mumps and western equine and St. Louis encephalitis were negative. Nearly half of the 25 paralytic illnesses associated with Coxsackie virus infection were in children aged 5 to 9 years.

Western equine encephalitis may overwinter in snakes

The method by which the virus of western equine encephalitis maintains itself during the winter months has long puzzled epidemiologists engaged in the study of this disease. Although it is established that birds play a part in its dissemination during the summer, their role as a winter reservoir host or as a means of reintroducing the virus into northern areas each year needs further clarification. The observation by Drs. Leo A. Thomas and Carl M. Eklund of the National Institute of Allergy and Infectious Diseases' Rocky Mountain Laboratory that *Culex tarsalis* overwinters in rockpiles along with hibernating garter snakes, led to speculation on the possibility of a snake reservoir. Preliminary tests demonstrated the susceptibility of the reptiles to WEE virus infection with a resulting viremia of high titer and long duration.

The present study further clarifies the problem and indicts garter snakes as one possible overwintering mechanism for the WEE virus. Findings were reported in the "Proceedings of the Society for Experimental Biology and Medicine."

In the experiment, the investigators inoculated 50 wild garter snakes intraperitoneally with virus-infected mouse brain suspension in September and November of 1959. The snakes were then placed inside a specially constructed cage and allowed to hibernate under simulated natural conditions.

During March, April, May, and June the snakes reappeared and after a short period, virus was detected in their blood in high titer for periods up to 70 days following emergence.

The scientists identified virus in 16 inoculated snakes and complete virus transmission from snakes though mosquito to chick was shown in 4. For transmission, uninfected *C. tarsalis* mosquitoes were fed on the posthibernating snakes with viremia and held from 9 to 23 days before being allowed to feed on a noninfected 1-day-old chick. In the four cases of demonstrated transmission, virus was isolated from the mosquitoes fed.

Although the data demonstrate a possible overwintering mechanism of WEE virus, Dr. Thomas notes that more conclusive evidence will be available if virus is isolated from garter snakes actually collected in the field.

ALLERGY-IMMUNOLOGY

Fluorescent antibody used to diagnose whooping cough

The use of the fluorescent antibody method as laboratory confirmation of pertussis is reported in the New England Journal of Medicine by Drs. Jo Anne Whitaker, Paul Donaldson, and John D. Nelson, of the University of Texas Southwestern Medical School. Based on their study of 128 patients, the investigators believe this test may replace examination by culture, which is time-consuming, difficult and, in many laboratories, yields as low as 20 percent positive cultures.

In this study positive fluorescent antibody smears from pernasal pharyngeal swab specimens were obtained in 78 percent of the patients using antiserum against B pertussis produced in rabbits, the globulin fraction of which was conjugated with fluorescein isothiocyanate. Positive results increased to 94 percent when only patients who had not received antibiotics and whose symptoms had been present less than 3 weeks were considered.

In 18 patients who received broad spectrum antibiotics for more than 48 hours, positive results fell to 11 percent. When the illness had persisted for more than 3 weeks before testing, only 57 percent of 14 patients were positive by fluorescence.

In contrast, a group of 36 normal infant controls were negative, and of 86 patients with a variety of respiratory infections other than pertussis, all were negative except 2. Those two were chronically ill with cardiorespiratory disease and had been exposed to pertussis. The investigators believe they may have had a mild or modified attack.

Positive fluorescent antibody results were obtained in all patients examined in the preparoxyamal stage of the disease. In one case an asymptomatic 2-month-old infant whose sibling had pertussis was also positive. Hyperimmune pertussis antiserum and tetracycline were given and the baby remained well in the face of illness of three remaining siblings. The investigators suggest that the fluorescent antibody method may be of especial value in detecting pertussis in asymptomatic infants in time to give prophylactic therapy that will prevent the disease in the very young who are susceptible to the most severe attacks.

Growth inhibition by hormones measured in asthmatics

A study of 19 children with intractable perennial bronchial asthma shows that prolonged treatment with adrenal cortical hormones has a measurable growth-inhibiting effect which is, however, reversible by discontinuing therapy or by reducing dosage below a critical growth suppressive level. This investigation at the Pediatric Allergy Clinic of the Johns Hopkins Hospital, supported in part by the National Institute of Allergy and Infectious Diseases, is reported by Drs. T. E. Van Metre, W. A. Niermann, and L. J. Rosen in the "Journal of Allergy."

Over a 5-year period a comparison was made of the growth inhibiting effect of prolonged treatment with a variety of adrenal cortical hormones, including cortisone, prednisone, methylprednisolone, triamcinolone, and fluprednisolene.

The study indicated that cortisone is about one-fifth to one-sixth as potent as prednisone and methylprednisolone as a therapeutic agent in asthma but only one-tenth as potent as a growth inhibitor. These relationships probably explain why children who received enough cortisone to suppress asthma grew normally while those receiving enough prednisone, methylprednisolone, triamcinolone and fluprednisolone to produce a similar suppressive effect usually grew at a retarded rate.

The drugs were given alone or in sequence more or less continuously for 6 months or longer to children ranging in age from 8 months to 9 years. In every case effort was made to use the least amount of drug that would control asthma. To minimize steroid damage, supplementary therapy as indicated in individual cases included allergen avoidance, desensitization, bronchodilators, expectorants, and antibiotics.

Before onset of corticosteroid therapy, linear growth rate was essentially normal. Therapy with prednisone or methylprednisolone inhibited growth when the average dosage for 6 months or longer exceeded 5.0 mg. per square meter of body surface per day, and growth was normal when the average dose was less; growth retardation was evident also during therapy with triamcinolone and fluprednisolone.

In contrast, linear growth was normal or accelerated when cortisone was used in dosages equivalent in predictable anti-inflammatory effect to those employed with the other steroids, and equally good control of asthma was obtained with these dosages.

The authors found that linear growth retardation was not observed in any asthmatic child receiving cortisone but was the rule in those receiving prednisone, methylprednisolone, triamcinolone, and fluprednisolone. With cortisone, normal growth was obtained even with dosages exceeding 55 mg. per square meter per day, although it seems probable from the work of others that higher dosages would cause growth suppression.

Guillain-Barre syndrome result of tetanus antitoxin

The Guillain-Barre syndrome, also known as acute idiocathic polyneuritis, infectious polyneuritis, Landry's paralysis, acute polyneuritis with facial diplegia and poly radiculoneuritis, is an acute disease of the central nervous system characterized by a rapidly progressing and often fatal paralysis beginning in the muscles of the feet and gradually ascending to other muscles of the body. Its causation has been obscure but the second report of a case following administration of tetanus antitoxin suggests the importance of an allergic mechanism in its etiology.

The report stems from a clinical study of a patient admitted to the Youngstown (Ohio) Hospital Association July 31, 1958, 1 week after receiving 0.5 cc. of undiluted tetanus antitoxin for a rusty nail wound to her hand. Upon admission she was unable to walk and complained of pain in the back, numbness of the hands and face and a feeling of heaviness in both arms. During her hospital stay until September 6 of the same year she manifested classic symptoms of the ascending paralytic disease. Following examination showed several sequelae of the disease.

Specimens of her serum showed extremely high titer of hemagglutinating antibodies against horse serum which persisted for at least 222 days. A titer of 1:32,000 was demonstrated on the 153d hospital day, 1:12,000 on the 222d day. This very striking antibody high titer response to a relatively small dose of antiserum may be related to the fact that the patient had received antiserum at the age of 6 or 7, some 30 years previously. Her medical history otherwise showed only mild reactions to penicillin injections and a pork allergy. There was no family history of allergy.

The authors, Dr. William D. Loeser, et al., of the Youngstown Hospital, submit that this case and another reported in 1958 by Dr. C. Arbesman and associates, while not establishing the etiology for all cases of Guillain-Barre syndrome, certainly suggest a hyperimmune response to horse serum as the causative agent for at least this segment of cases. Their study, supported in part by a grant from the National Institute of Allergy and Infectious Diseases, is published in "Neurology."

New antigen may cause rejection of tumor

Evidence to date points to the presence of a new tissue antigen in mouse polyoma tumor that differs from that present in normal mouse tissues. Dr. Karl Habel, Chief of the Laboratory of Biology of Viruses of the National Institute of Allergy and Infectious Diseases, has reported at the federation meetings in Atlantic City that this different antigen acts as a foreign substance to which the normal immunologically competent adult animal reacts.

Dr. Habel postulates from his studies of the mouse polyoma virus that when this virus causes tumors in newborn animals these young animals, being immunologically immature, do not recognize the new antigen as foreign. Thus they become tolerant to it and allow the tumor to develop. When virus is inoculated into the adult animal, some cells are also transformed to tumor cells but the immunologically competent adult recognizes the new tumor antigen as foreign and rejects it. In the process of this rejection in which no tumor develops, the adult mouse becomes sensitized to the new antigen, thus allowing more efficient rejection by the animal of the transplanted tumor with its same foreign antigen when it is inoculated later.

Resistance to supporting the growth of the transplantable tumor is relative and can be overcome by a large dose of transplanted tumor cells. Furthermore, resistance seems to be specific against only tumors originally produced by the polyoma virus. It appears to reside in the cells of the virus-immune adult and is not based on antibodies against the virus itself which are in the blood.

The hypothesis that there is a new tissue antigen in mouse polyoma tumors which immunologically immature animals do not recognize would explain why the same virus infecting a very young animal results in tumors but in adults causes only inapparent infection with no tumors.

Inbred guinea pigs develop allergic thyroiditis

Allergic thyroiditis has been produced experimentally in a strain of inbred guinea pigs for the first time by scientists at the National Institute of Allergy and Infectious Diseases. The results of the experiment are reported in the "Journal of Experimental Medicine."

Dr. Phillip R. B. McMaster, Dr. Edwin M. Lerner, II, and Mr. Eurmal Exum were able to produce an allergic inflammation of the thyroid by injecting strain 13 guinea pigs with extracts of thyroid glands of other guinea pigs of the same strain.

The disease appeared in some animals as early as 5 days after injection and is the earliest recorded occurrence of experimental thyroiditis. Severe damage to the thyroid gland was found at later stages, and has been found as long as 6 months after immunization. By using the strain 13 guinea pig extract and Freund's adjuvant, it was possible for the scientists to produce the disease in severe form and at very early periods with only a single injection.

When the scientists skin-tested the animals they found delayed hypersensitivity as early as 5 days after injection, and such hypersensitivity was present in all animals with thyroiditis at 7 weeks. It was found in some animals as late as 6 months after immunization.

Human sera reaction demonstrated by fluorescent antibody

For several years it has been known that sera from patients with certain diseases, particularly lupus erythematosus, have antinuclear activity. When a patient's serum is incubated with human or other mammalian cells, gamma globulin in the serum reacts with the nuclei of the cells. If the cells then are incubated with fluorescent-labeled antihuman globulin, the nuclei will fluoresce under ultraviolet light. The discovery that certain sera, having antinuclear activity, also react with human and other mammalian chromosomes is reported in "Science."

The authors are Dr. Robert S. Krooth, working at the National Institute of Allergy and Infectious Diseases on loan from the National Institute of Neurological Diseases and Blindness, Drs. John E. Tobie and Howard C. Goodman of the National Institute of Allergy and Infectious Diseases, and Dr. J. H. Tjio of the National Institute of Arthritis and Metabolic Diseases.

Sera from patients with lupus erythematosus, Sjögren's syndrome and nephrosis first were tested for antinuclear activity by the investigators. All sera reacted with mouse liver nuclei when tested by the fluorescent antibody technique. The sera were then allowed to react with cromosomal preparations made from human peripheral blood cells and a variety of other human and subhuman mammalian tissue culture cells; subsequently, the chromosomes were stained with fluorescein-labeled horse antihuman globulin.

Serum from five of six patients with systemic lupus erythematosus (SLE) reacted with chromosomes, as indicated by chromosomal fluorescence. Most of the sera possessing such antinuclear activity apparently had reacted with all of the chromosomes of the cells, since 46 discrete fluorescent chromosomes were usually observed. When, after fluorescent staining, the same cell was restained with acetic acid-orcein, every chromosome staining with fluorescent antibody also stained with orcein.

Serum from one of two patients with nephrosis also reacted with chromosomes of all of the mentioned cell types when examined by this method. However, serum from the three patients with Sjögren's syndrome could not be demonstrated to react with chromosomes, even though clear evidence that it possessed antinuclear activity could be demonstrated by its positive reaction with mouse liver cell nuclei.

In the light of these findings, the authors suggest that perhaps certain sera may be found which are more specific in their chromosomal reactions. The authors also suggest additional studies directed to the determination of the nuclear antigens involved in these reactions so that the significance of antinuclear factors, found in the sera of patients with diseases such as lupus erythematosus, can be better understood.

The front cover of this issue of "Science" features the authors' photomicrograph of the 46 chromosomes of a human cell stained with fluorescent antibody.

PARASITIC DISEASES

Malaria occurs naturally in rhesus monkeys

Laboratory findings reported in "Science" contravert the widely held belief that rhesus monkeys are free of naturally acquired malaria. The authors acknowledge that the belief—backed as it is by some 30 years of careful investigations—cannot be dismissed lightly.

Between 1945 and July 1960, some 5,600 rhesus monkeys were examined by Dr. Leon H. Schmidt and coworkers at Christ Hospital Institute of Medical Research, Cincinnati, and not one natural occurrence of malaria was observed. A first occurrence on the latter date consequently was attributed to an undefined "laboratory accident."

In January 1961, prior to initiation of a malaria experiment, thick blood films were prepared on 79 of a shipment of 100 rhesus monkeys which had arrived from Pakistan in the latter part of 1960. Blood films were examined routinely for the presence of parasites—a practice which for years has yielded negative results. To the amazement of the investigators, seven specimens proved positive. Immediate examination was made of later shipments from Pakistan; 22 of 228 rhesus monkeys were found to be naturally infected.

In the majority of subjects a single species of plasmodium appeared to be involved. In two cases there were evidences of multiple infections. Identification of the plasmodial species is still in progress. In the majority of cases data suggest that the parasite is the morphologic counterpart of the Institute's stock strains of *Plasmodium inui*. In the two cases suggestive of multiple infections, a plasmodium similar to *P. cynomolgi* also appears to be involved.

The investigators suggest that conflict between their observations and earlier findings probably is related to the area from which the animals were obtained. For many years the majority of rhesus monkeys have come from areas adjacent to Lucknow. Although there is no certainty in this matter, the animals recently imported from Pakistan may have been obtained near the Burma-Assam border, where they could have been in contact with other species of monkeys (*Macaca cynomolgus* or *M. nemestrina*) in whom malaria is well known to occur naturally.

Strain of malaria proved resistant to chloroquine

Resistance of human malaria to chloroquine has been definitely shown for the first time in a strain of *Plasmodium falciparum* which gave a poor response to normal and above-normal doses of chloroquine. A study of this strain of malaria is reported in the American Journal of Tropical Medicine and Hygiene by Dr. Martin D. Young of the Laboratory of Parasite Chemotherapy, National Institute of Allergy and Infectious Diseases, and Dr. Donald V. Moore of the Southwestern Medical School of the University of Texas.

Infected blood from a patient in Colombia, South America, who had not responded to chloroquine treatment of malaria, was used to induce the disease in eight patients. The resulting infection was treated with chloroquine diphosphate given in oral doses of 150 milligrams and of 600 milligrams, as well as the standard 1.5-gram dosage over a 3-day period . With the exception of one case, the parasites either were not removed, or, if removed the infection relapsed shortly thereafter.

The parasitemias of susceptible strains disappear in less than 3 days by 1.5 grams chloroquine, with a relapse rate of less than 2 percent. Most of the Colombia strain infections treated with this dosage were either removed more slowly than the susceptible strains or not cleared at all. Furthermore, of the four cleared by 1.5 grams or 2.1 grams, three relapsed in 9 to 18 days.

In 622 cases of malaria from North America and Malaya the parasitemias due to normal (susceptible) strains are eliminated in 3 days or less by either 0.4 gram or 0.6 gram chloroquine given in a single oral dose. None of three patients with the Colombia strain was cleared by 0.6 gram. The fact that the drug was given under close supervision, that the urines gave a positive Haskins test for chloroquine, and that the plasma levels of the chloroquine were at therapeutic concentrations eliminates any doubts that the drug was being delivered to the parasites in the bloodstream.

Because of the widespread use of this drug for the suppression and cure of malaria and especially in malaria eradication programs, where it has been in effective use since World War II, the occurrence of resistance by the parasites appears to be of considerable importance.

Natural vector of simian malaria identified in Malaya

A mosquito that transmits malaria to monkeys in nature has been identified and reported for the first time by Drs. R. H. Wharton, Institute for Medical Research, Kuala Lumpur, Federation of Malaya, and Dr. Don E. Eyles, Laboratory of Parasite Chemotherapy of the U.S. Public Health Service, National Institute of Allergy and Infectious Diseases. Their report, appearing in the current issue of Science, marks the first demonstration of a natural vector of any monkey malaria. Whether this species, *Anopheles hackeri*, also transfers simian malaria to man remains to be proved.

The problem of transmission of this malaria in nature is under intensive investigation as a followup to the discovery last year by Dr. Eyles and his colleagues, also reported in Science, June 17, 1960, that monkey malaria is transmissible to man. This fact has disproved the long-held concept of malaria investigators that types of malaria infecting lower animals cannot be inoculated successfully into man by the bite of an infected mosquito.

Until comparatively recently, the *A. hackeri* mosquito was regarded as a rather rare species breeding in the split bamboos in inland forest. It is now known, however, to be quite common on the Selangor coast of Malaya.

Mosquitoes were caught in an open net trap, baited with monkeys, on a platform 20 feet above ground level. Over a period of 34 nights, 20 *A. hackeri*, including 17 which contained blood, were captured. Four without blood were taken in a similar trap on the ground. Tests with blood from freshly fed mosquitoes confirmed that *A. hackeri* was feeding upon monkeys.

In a search for the parasite which causes malaria, over 700 mosquitoes were dissected to find 1 sporozoite infection—the phase of the developmental cycle when the parasite becomes infective for its vertebrate host. An uninfected Indian rhesus monkey was inoculated intravenously with the sporozoites. Six days later small ring forms were seen sparsely in the blood. The infection built up so rapidly that the monkey died 3 days later. The parasites which caused the malaria were identified as *Plasmodium knowlesi, a* common form of simian malaria.

Parasitic infections place man in double jeopardy

The "double jeopardy" to man of parasitic infections which also cause hypersensitivity demands parasitologists with knowledge and training in immunology equal to competence in their primary field, Dr. Andrews stated in his presidential address before the American Society of Parasitologists in Lafayette, Ind., August 29.

"Little is known about the actual incidence of allergic morbidity and mortality due to hypersensitivity to helminth parasites," the Director of the National Institute of Allergy and Infectious Diseases said, "but certainly some of these possibilities are of more than academic interest."

Dr. Andrews indicated some of the possibilities, as well as realities, of allergic illness and disability due to a hypersensitivity to worm parasites and explained procedural devices for indicating the existence of allergic state in parasitic diseases.

Mentioned in the address were some of the "many new ideas and techniques which can be developed or applied by parasitologists, hopefully to solve some of the problem areas of immunology—especially hypersensitivity—as these are involved in parasitic disease." Dr. Andrews listed the following areas of possible research:

1. Parasite antigens, like other antigenic substances, should be characterized and standardized—so that observations made by different investigators may have common, dimensionable, and reproducible bases.
2. To achieve standardization, it will doubtless be necessary to utilize new and novel techniques for the purification of parasite antigens. Conceivably, these might include, among others, such procedures as paper and ion-exchange chromatography, starch-block electrophoresis, sonic disintegration, the separation of cell wall and cell contents by decompressive methods, and the isolation of intracellular bodies which may be of significance.
3. Basic studies should be made of the chemical and physical properties of parasite antigens.

4. Simplified and more adequate passive transfer techniques should be devised, and studies made re the immediate and delayed types of hypersensitivity observed in parasitic diseases. It is not improbable that tissue-culture techniques might be found useful in this connection.

5. Comprehensive studies should be made of the chemical and physical properties of skin sensitizing antibodies found in parasitized individuals and lower animal hosts—and of the other components responsible for specific skin reactivity.

6. If and when new and more sophisticated techniques become available which are appropriately applicable to the problems of the immunology of parasitic infestation, parasitologists might be well advised to repeat some of the older research in this field to ascertain whether or not it can be confirmed.

New freezing method preserves live protozoa

In a paper presented to a meeting of the American Society of Parasitologists at Purdue University, Lafayette, Ind., Dr. L. D. Diamond of the National Institute of Allergy and Infectious Diseases' Laboratory of Parasitic Diseases, reported the success of the new method in tests performed with the parasite *Entamoeba histolytica*, the organism that causes amebiasis. Dr. Diamond and his coworkers, Dr. H. T. Meryman and Mr. E. Kafig of the Naval Medical Research Institute, National Naval Medical Center, developed the method to facilitate Dr. Diamond's parasitic disease studies.

They found that slowly freezing the one-celled animals and then coldstoring them in liquid nitrogen has preserved them intact for at least 7 months. Experience of other investigators showed that this method preserved other types of cells at least 6 years. When required, the frozen entamoebae need only be thawed and they are ready for use. The liquid nitrogen method provides laboratory investigators with an economical and efficient method of storing certain live protozoa, some of which cause severe and dangerous infections.

Canine schistosomiasis seen in Western Hemisphere

The discovery that the dog is a host of *Heterobiltharzia americana*, a species of schistosome, was made in the course of an investigation into the possible role of zoonotic schistosomiasis in producing a severe dermatitis observed among trappers, oilfield workers, and others by Burks and Jung in 1960. The dermatitis was apparently acquired from wading in the swamps of southern Louisiana.

Drs. Emile A. Malek, L. R. Ash, H. F. Lee, and M. D. Little, of Tulane University School of Medicine, supported by a grant from the National Institute of Allergy and Infectious Diseases, examined snails, birds, and mammals from the Mississippi River Delta and the marshy coastal areas of Louisiana. Results of the examination appear in the Journal of Parasitology.

The investigators found *H. americana* in 25 of 52 raccoons, 22 of 37 nutrias, and 3 of 3 dogs, indicating a wide range of hosts. In all these mammals the host-parasite relationship appeared to be well established. This was evidenced by the large number of viable eggs discharged with the stools and the numerous worms recovered at autopsy.

Pronounced symptoms were associated with an advanced, heavy infection in one of the dogs; however, these symptoms were not observed in the two other dogs with moderate or light infection. The heterobilharziasis found in the dogs is the first canine schistosomiasis recorded for the Western Hemisphere. The authors are of the opinion that it may prove to be an important disease of dogs in some parts of the Southern States.

In addition to canines and rodents, *H. americana* is known to occur naturally in felines. The relationship of this schistosome to the dermatitis observed in man has not yet been established. The authors say that the cercariae, the free-swimming larvae, could perhaps penetrate the skin, and that the schistomulae, the preadults possibly could invade the lungs and liver.

Iodine effectively disinfects vegetables

In regions of the world where human feces are used for fertilizer, vegetables may be contaminated simultaneously with infective stages of Ascaris, hookworms, and other helminths. Although a number of chemicals kill such parasites, no agent has been acceptable for use as a disinfectant of fresh vegetables. Supported by a grant from the National Institute of Allergy and Infectious Diseases, Prayith Thitasut, of Tulane University (now with the Siriraj Hospital Medical School, Bangkok, Thailand), conducted investigations to determine the concentrations of aqueous solutions of iodine required to kill the infective stages of

Necator americanus, Ancylostoma caninum, Strongyloides stercoralis, Ascaris lumbricoides, Toxocara canis, and *Trichuris muris.*

The results of the investigation appear in the American Journal of Tropical Medicine and Hygiene. Solutions used were prepared by dissolving commercially prepared tablets in distilled water. Different concentrations were required to kill the infective free larvae of hookworms and *Strongyloides* and infective larvae in the eggs of *Ascaris, Toxocara,* and *Trichuris.* Killing action was more rapid at low than at high temperatures. Solutions at concentrations up to 500 parts per million did not adversely affect the flavor or appearance of any of the common types of leafy or rooty vegetables.

Solutions of sufficient strength to kill the eggs and larvae of these worms, and at the same time to destroy the common enteric micro-organisms, are easily prepared and therefore appear to be suitable for the disinfection of vegetables to be consumed in the fresh state, the investigator says. He also notes that aqueous solutions of iodine are used in disinfecting food utensils and are known to be less irritating to the mucous membranes than are chlorine and other chemicals.

The investigator cautions, however, that practical application of his test procedures cannot be taken for granted. On contaminated fruits and vegetables, eggs, larvae, and other infectious organisms might be protected from the action of iodine by waxes and other substances. He recommends that precautions be taken to remove protective particles and masses from the vegetables and to expose all surfaces to the disinfectant.

Schistosomiasis reported for first time in Lebanon

In Lebanon, where schistosomiasis has never previously been reported, 14.6 percent of close to 600 individuals tested had clinical evidence of that parasitic disease. The investigation of this first focus of schistosomiasis in that country is reported in the American Journal of Tropical Medicine and Hygiene by Drs. J. E. Azar, G. W. Luttermoser, and J. F. Schacher, department of tropical health, American University of Beirut, Lebanon. Dr. Luttermoser, on leave from the Laboratory of Parasite Chemotherapy, National Institute of Allergy and Infectious Diseases, is teaching and doing research at Beirut.

Schistosomiasis, a disease highly prevalent in many countries of this region, has at no time previously been reported in the indigenous Lebanese population. Upon discovery of a single case, a field study was begun. Single urine specimens were collected at random from 591 residents, 171 from children in schools and the remainder from children and adults interviewed during house-to-house visits.

Infection by the blood flukes which cause schistosomiasis is acquired by penetration of aquatic larval forms through the skin. Intermediate hosts of these small worms are various species of snails which live in fresh water. The two chief sources of surface water available to the village are a spring at the base of a hill and the Kasmiye-Litani Canal. The canal, which has been operating in the area since about 1953, is a relatively new factor in the life of the community and is probably the chief source of fresh water for the people living along its banks. Examination of the spring gave no indication that it was a suitable habitat for snails, but on the banks of the canal numerous snail shells of the species *Bulinus* (*Bulinus*) *truncatus* Audouin were found. No living snails of that species were found in the course of investigation, but live snails of five other types were recovered.

The short history of clinical signs of schistosomiasis revealed during questioning leads the investigators to believe that the disease has only recently been introduced into the study area. Resettlement of infected populations in areas previously uninfected has favored the introduction of the disease where it had not existed before, and new irrigation projects have favored the spread of the disease by creating favorable habitats and vehicles for the snail intermediate host. In the light of present and projected irrigation schemes in Lebanon, the investigators believe that the finding of schistosomiasis is of public health importance. Although their study is geographically limited, the scientists feel that chances are good that schistosomiasis exists throughout the wide area of irrigation served by the canal.

Ovine toxoplasmosis in New Zealand sheep described

The sources of human toxoplasmosis infection are far from clear, and the problem of congenital transmission, which has been occurring in New Zealand sheep, is intriguing. Research on this problem in New Zealand by Dr. Leon Jacobs, Chief of the Laboratory of Parasitic Diseases, National Institute of

Allergy and Infectious Diseases, was undertaken to complement studies in Bethesda, as well as to aid the New Zealand Government. Dr. Jacobs, who made his studies under a Fulbright scholarship, reported his findings to the American Society of Tropical Medicine and Hygiene.

A great deal of infection was found in New Zealand sheep, and it was possible to obtain data on the rate of infection in a small mob of animals; this was also high. By the time the animals are 2 to 2½ years old, most have already picked up the infection. Toxoplasma-induced abortion occurs most frequently in younger animals, which are about 18 months old when they are mated for the first time. Adult animals showed no ill effects from infection with millions of parasites, except for a fever of only a few days' duration. However, abortion or diseased lambs resulted when animals were infected by a variety of routes, from intravenous inoculation to intranasal instillation or oral administration of parasites, but only when the infection was given during the pregnancy. Infection prior to pregnancy did not result in abortion. Animals that were naturally immune, as revealed by the presence of antibodies in their serum, resisted artificial infection and had a higher percentage of healthy lambs than nonimmune animals. Similarly, animals that were infected prior to pregnancy and then challenged with another infection during pregnancy gave birth to healthy lambs, while the control ewes infected only during pregnancy experienced abortion and related disease of the lambs. However, immunity could be overridden with large doses of parasites in the "challenge" infection.

Dr. Jacobs believes that in nature it is unlikely that infection is initiated by enormous doses of organisms, so there is hope that immunity can be developed by vaccinating sheep prior to pregnancy. This and other factors indicate work on immunization should be undertaken, but it must await the development of good antigens before it can be started. This work is presently underway.

The method by which sheep and other herbivorous animals acquire toxoplasmosis is still not known. Experiments underway now in New Zealand, suggested by Dr. Jacobs, may aid in solving this point.

Regarding the circumstances of congenital transmission, it appears that the ewe must experience the acute stage of the infection during pregnancy to have an abortion. This is what the general clinical experience has been in human beings. The mothers of babies afflicted with toxoplasmosis generally have healthy babies in subsequent pregnancies. This has been questioned, but thus far no proof has been obtained to show that chronically infected mothers can transmit the disease to a foetus in utero.

Complication of schistosomiasis studied in laboratory

In mice, it has been found possible to produce splenomegaly, one of the severe complications of schistosomiasis, with as few as one or two pairs of worms. The finding was presented by Dr. Kenneth S. Warren, Laboratory of Parasitic Diseases of the National Institute of Allergy and Infectious Diseases, at the recent meeting of the American Society of Tropical Medicine and Hygiene.

Severe hepatic fibrosis resulting from infection with *Schistosoma mansoni*, the worm parasite which causes schistosomiasis, impedes blood flow from the spleen with the result that so-called congestive splenomegaly occurs. In spite of much human and animal investigation, the exact way in which the worm *S. mansoni* causes this disease has remained in doubt.

Recently a syndrome in mice resembling splenomegaly in humans has been reported from the Laboratory of Parasitic Diseases, and studies on its etiology have been undertaken in the laboratory. Previous experiments which produce the syndrome in test animals involved fairly heavy worm infections, comparable to approximately 70,000 worms per adult human. To determine whether the condition could be produced by smaller worm burdens, animals were infected with 161, 112, 73, and 28 cercariae of a Puerto Rican strain of *S. mansoni*, and it was found that as few as 1 or 2 pairs of worms per mouse caused splenomegaly. In these animals also, the development of the complication is greatly delayed, beginning at 20 to 25 weeks rather than at 10 weeks as in mice with greater worm burdens.

Dr. Warren believes that further study of this dangerous complication of schistosomiasis in a laboratory model may lead to additional fundamental knowledge that can be applied to the human disease, an affliction borne by more than 150 million people.

Good nutrition has favorable effect against schistosomiasis

The result of a 15-month study by Dr. W. B. DeWitt of the Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, with the collaboration of Dr. Jose Oliver-Gonzales of the University of Puerto Rico and Dr. Eduardo Medina of the Rio Piedras Municipal Hospital, Puerto Rico, was reported at the recent meeting of the American Society of Tropical Medicine and Hygiene.

The effects of diet in laboratory animals infected with *Schistosoma mansoni* has been the subject of considerable experimentation in the Laboratory of Parasitic Diseases. When mice were fed a diet grossly deficient in nutrients it was found that disease due to the schistosome infection did not develop at the expected rate; when fed a balanced diet, severe disease developed rapidly. These surprising results led the investigators to design a comparable experiment in the human host.

In distinct contrast to the results in laboratory mice, all patients—34 young adults infected with *Schistosoma mansoni* who had previously subsisted on a diet low in protein and deficient in vitamins—when on the improved diet showed marked benefits from good nutrition in combating the disease processes associated with schistosomiasis. Vitamin levels in serum protein and in urine were measured and liver function tests were performed. Height as well as weight approached normal in the subjects on the diet during the test period, and increased physical well-being of each patient was evident. In every case laboratory and physical examinations confirmed improvement directly referable to the test diet.

BACTERIAL DISEASES

Urine culture aids diagnosis of urinary tract infections

In a study at the University of Utah College of Medicine, supported in part by the National Institute of Allergy and Infectious Diseases, Dr. Paul D. Hoeprich has developed a technique by which it is possible to count bacteria precisely enough to group the counts into categories significant in the diagnosis of urinary tract infection. His work is reported in the Journal of Laboratory and Clinical Medicine.

Using a standard, volume-calibrated bacteriologic loop of the kind commonly employed in dairy bacteriology, quantitation of bacteriuria has been accomplished that compares favorably with the classical dilution-pour plate method, which is too expensive of time, personnel, and materials for routine use in the clinical laboratory.

Quantitative culture of the urine is a necessity in the diagnosis of urinary tract infections. Although relatively asymptomatic, these infections have potential for cardiovascular and obstetrical complications and eventual renal failure in untreated cases. In this country, urinary tract infections are the most frequent of infectious diseases next to respiratory infections. With the new technique, it is possible to quantitate bacteriuria into the three categories known to be significant in diagnosing urinary tract infections; fewer than 10,000 bacteria per milliliter of urine (infection unlikely); between 10,000 and 100,000 (infection probable); more than 100,000 (infection almost certain).

The reliable demonstration of true bacteriuria is the mainstay of diagnosis of urinary tract infections, which can be controlled by a variety of broad spectrum antibiotics in the early, uncomplicated stages of infection. Calibrated loop streak plate culture, as described by Dr. Hoeprich, is both simple enough for general use and precise enough to support diagnosis and therapy of urinary tract infections.

Alpha toxin of staphylococcus acts selectively

Alpha toxin, the powerful necrotizing agent produced by staphylococcus, is very probably important in the pathogenesis of localized staphylococcal disease and the shocklike picture sometimes associated with staphylococcal septicemia. However, its precise role in abscess formation is unclear; nor has it been clear whether it acts as a general cellular poison or selectively on the smooth muscle cells.

Experiments by Dr. Alan P. Thal and Willadene Egner, of the University of Minnesota Medical School, demonstrate that epithelial cells in tissue culture and isolated preparations of living cardiac and skeletal muscles are resistant to the action of the toxin. On the other hand, the studies show that smooth muscle, regardless of its origin, appears to be exquisitely sensitive to the toxin and is irreversibly damaged by its action in a few seconds. The findings are reported in the Journal of Experimental Medicine.

Previous studies by the NIAID grantees had suggested that the toxin had a selective effect on vascular smooth muscle. Their latest experiments, employing toxins derived from pathogenic human strains, add the following observations:

(1) The toxin produces an immediate hyperperistalsis and sustained increase in intraluminal tension progressing ultimately to atony and flaccid paralysis in the isolated smooth muscle preparation.

(2) The addition of specific antitoxin prior to exposure to toxin prevents this reaction. However, when antitoxin is added after the toxin, no ameliorating effect is seen.

(3) The toxin is rapidly and irreversibly bound to its substrate, since washing a bowel segment 30 seconds after exposure to toxin fails to change the course of the reaction.

(4) When the toxin is infiltrated in the neighborhood of muscular blood vessels in the living rabbit, selective necrosis of smooth muscle cells of the vessel walls is seen.

(5) The selective effect on smooth muscle is emphasized by the failure of the toxin to affect the contractility of skeletal and cardiac muscle.

(6) Selectivity is also emphasized by the fact that epithelial cells and fibroblasts in tissue culture, exposed to high concentration of toxin for 2 hours, are unaffected in their ability to recover and metabolize.

Control studies were made by the investigators to eliminate possible production of biologic effects on smooth muscle from culture media, endotoxic derivatives of cell walls, or histamine like substances.

Secondary spread of drug-resistant tuberculosis surveyed

Present public health measures may have to be reevaluated as a result of a recent large-scale survey definitely linking isoniazid-resistant tubercle bacilli to initial childhood tuberculosis. More specifically, the common practice of returning a parent to the family, simply because he or she is receiving therapy, may have to be abandoned.

The survey was undertaken by the committee of the Section on Diseases of the Chest, American Academy of Pediatrics, in cooperation with clinics caring for tuberculous children. It is the first report of initial infections among children with isoniazid-resistant tubercle bacilli in the United States. A detailed analysis of the committee report has been made by Drs. Charlotte M. Zitrin and Edith M. Lincoln, grantees of the National Institute of Allergy and Infectious Diseases, and appears in the Journal of Pediatrics.

Although streptomycin-resistant strains are unmistakably associated with clinical and X-ray relapse, as well as reconversion to positive sputum, many patients harboring isoniazid-resistant strains continue to do well clinically. A report in 1954 by Dr. Gardner Middlebrook attempted to explain this phenomenon by observing that tubercle bacilli, in the course of becoming isoniazid resistant, lose the action of the enzyme (catalase) normally present. The loss of this action was apparently associated with the loss of virulence. Other reports demonstrated, however, that isoniazid-resistant strains of bacilli may produce lethal tuberculosis in both the guinea pig and mouse.

In recent years, studies have been made on previously untreated adults infected with isoniazid-resistant organisms. These suggest that the organisms can be virulent for man even though attenuated in animals. The authors point out, however, that in considering the findings in adults, it should be borne in mind that it may be difficult to prove that these infections are, in fact, primary.

The present investigation was undertaken among children with primary tuberculosis, in whom the possibility of reinfection would not be a factor. The survey covered 7 clinics with a total of 2,500 patients seen since the introduction of streptomycin therapy. Of these, 1,800 were patients examined since the beginning of isoniazid treatment. Approximately 325 initially positive cultures (i.e., pretreatment) were obtained from the patients since the introduction of streptomycin therapy, 235 since that of isoniazid. Of this total, 6 were found resistant to streptomycin, 2 to isoniazid, and 5 to both streptomycin and isoniazid, making a total of 13 patients resistant to one or both drugs. In three of these instances, the contact was known to have been resistant to the same drug as the infected child. The results are believed to establish the principle of infection in human beings with isoniazid-resistant organisms.

Cystic fibrosis cases misdiagnosed as respiratory allergy

The importance of considering cystic fibrosis in the diagnosis of patients with recurrent respiratory tract involvement is underlined in a recent study by Drs. L. L. Kulczycki (H. Mueller, and Harry Shwachman of Harvard Medical School. According to these scientists, the attending physician should also maintain an awareness of the possible coexistence of allergy in patients with cystic fibrosis. The authors of the report are grantees of the National Institute of Allergy and Infectious Diseases. Their findings are published in the Journal of the American Medical Association.

In this investigation, the scientists examined 266 patients with cystic fibrosis and confirmed the presence of allergy in 47 patients, with a predominance of respiratory allergy noted in 44 patients, or 16.6 percent. Although a number of the patients in this study had been treated at one time for respiratory allergy, more than half of them did not meet the requirements for this kind of diagnosis. In spite of many etiological, clinical, and pathological differences between asthma and cystic fibrosis, there are many similarities in the pulmonary manifestations of both conditions. In a patient with chronic respiratory manifestations, the diagnosis of cystic fibrosis may be overlooked and the clinical impression of allergy may be misleading, until the basic diagnostic procedures, such as sweat-electrolyte analysis and allergy skin tests, support the history and the clinical findings. On the other hand, the patient with cystic fibrosis may develop allergic manifestations, which should be investigated and treated concurrently.

The present study does not support reports by other investigators indicating that patients with respiratory allergy alone may also have elevated sweat-electrolyte levels. The authors point out, however, that parents of patients with cystic fibrosis, although presenting no clinical manifestation themselves, may manifest elevated sweat-electrolyte levels. This may be explained apparently on the basis of a carrier state for the gene of cystic fibrosis.

Pancreatic dornase useful in cystic fibrosis

Prior in vitro screening which would facilitate the selection of potentially therapeutic enzymes to treat pulmonary complications in cystic fibrosis is being investigated at Children's Hospital, Philadelphia. Drs. W. S. Chernick, G. J. Barbero, and H. J. Eichel have reported this study, aided by a National Institute of Allergy and Infectious Diseases grant, in Pediatrics.

The present study demonstrates that pancreatic dornase (deoxyribonuclease) markedly reduced the viscosity of secretions of cystic fibrosis, an effect anticipated to some extent by the investigators because of their earlier finding that tracheobronchial secretions contain a high concentration of DNA. Reduction in the DNA concentration in the secretions and parallel decrease in viscosity of the secretions emphasize the role of deoxyribonucleoproteins in contributing to the viscid properties of these secretions from cystic fibrosis patients.

To evaluate the in vitro effectiveness of pancreatic dornase and other enzymes on tracheobronchial secretions, specimens were obtained by bronchoscopy in 5- to 15-year-old patients with advanced pumonary involvement.

Spectophotometric analysis was done on the products obtained by incubation of the specimens with selected enzymes. This revealed that pancreatic dornase rapidly decreased the viscosity of the homogenate and also effected a considerable release of compounds having a maximum absorption at 270μ. Of nine other enzymes tested, only two (trypsin and chymotrypsin) caused appreciable hydrolysis of the secretions as reflected by absorption at $270\ \mu$, but these were only a third to a half as effective as dornase in reducing viscosity.

The investigators stress that the procedures they describe should serve only as a guide in the selection of potentially therapeutic agents because factors in the clinical situation are more complex than those of in vitro screening. Until controlled clinical studies can be analyzed, caution is advised in using dornase in routine treatment due to the many inherent dangers associated with its promiscuous use.

Furaltadone ineffective antibacterial

Studies supported by the National Institute of Allergy and Infectious Diseases confirm the lack of therapeutic or prophylactic usefulness of the drug known by the generic name furaltadone and by the trade name Altafur. The studies were conducted at Boston City Hospital by Drs. Clarke G. McCarthy and Maxwell Finland of Harvard Medical School and are reported in Archives of Internal Medicine.

The drug was first introduced in 1958 under the name "furmethonol." Since that time several papers have appeared dealing favorably with its antibacterial action in vitro, particular attention being given to the susceptibility of nearly all strains of *Staphylococcus aureus* including those resistant to the most widely used antibiotics.

The early claims were based on sensitivity tests employing "diagnostic discs" impregnated with furaltadone. The assumption used to interpret results was that inhibition of growth of any culture around such discs meant that the organism was susceptible to the drug in vivo. The grantees state that their investigations and those of several other investigators do not sustain this claim.

In a limited clinical study 2 to 6 days of furaltadone treatment was ineffective against severe staphylococcus and other bacterial infections in nine patients.

The grantees also report their observations on furaltadone antibacterial activity in serum. A total of 95 specimens of serum was obtained at various intervals during the course of furaltadone treatment of another group of 12 patients—during injections, immediately after completion of intravenous doses, and between such doses, and some also between oral doses. In not a single instance did serum from furaltadone-treated patients demonstrate any activity against a test staphylococcus. The failure to demonstrate activity in serum was not related to protein binding of the drug or to the method of preserving the specimens.

The suggestion that this drug be reserved for serious infections in patients in whom other drugs have failed or may not be expected to have favorable effect is most unfair, the grantees state. It implies a possible usefulness of the drug as a last resort but actually only tends to divert the physician from seeking other methods for which there may at least be some more reasonable basis for expecting useful effect, they add.

Two editorials critical of the claims made concerning the efficacy of furaltadone have appeared in the New England Journal of Medicine, one of which was carried as recently as the July 6, 1961, issue. Similar editorial comment has also been published by the British Medical Journal.

RICKETTSIAL DISEASES

Q fever organism can be grown in tissue culture

Excellent growth of *Coxiella burnetii*, causative organism of Q fever, has been obtained in studies reported in the American Journal of Tropical Medicine and Hygiene, by E. G. Pickens and J. A. Gaon, working at the Rocky Mountain Laboratory, Hamilton, Mont., field station of the National Institute of Allergy and Infectious Diseases.

In minced chick-embryo tissue and using a lactalbumin growth medium planted on a modified Zinsser's agar medium, the investigators achieved growth of the organism comparable to that in yolk sac of embryonated chicken eggs. Although the infectious titer of tissue cultures was considerably lower than in the older method, smears of the former always contained more rickettsiae than smears of the latter. The yield of purified rickettsiae isolated from four different lots of infected chick-embryo tissue culture varied from 0.7 to 1.2 milligrams per gram of original tissue, a yield comparable to that obtained from yolk sacs of infected embryonated chicken eggs, and antigenic activity was also comparable. These observations indicate that although the percentage of viable rickettsiae is lower, total growth in both methods compares favorably.

Using the new method, it was also possible to prepare satisfactory vaccines and antigens. Guinea pigs inoculated with a single 1 milliliter dose of vaccine prepared from tissue culture rickettsiae were completely immune when challenged 21 days later with 10^3 minimum infectious guina pig doses.

The investigators found that *C. burnetii* grows equally well in mouse-embryo tissue cultures. They suggest that this technique would be particularly useful in geographic areas where fertile hens' eggs are not readily available. Because the organism has remained viable in tissue cultures for as long as 110 days, this provides another means of maintaining strains where storage at freezing temperatures is not possible. Using the new tool, basic investigations of phase variation and morphologic entities can be undertaken.

FUNGUS DISEASES

Experimental drug effective in systemic mycoses

A new antibiotic derived from an unnamed species of streptomyces is reported to possess therapeutic value against several of the serious systemic mycoses. Its codiscoverers, Drs. Emanuel Grunberg and Julius Berger of Hoffman-LaRoche's Chemotherapy Laboratory, assigned the experimental drug a code designation, X–5079C. Trials in experimental mycoses by Dr. Chester W. Emmons, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, immediately confirmed the low toxicity and therapeutic activity observed by Drs. Grunberg and Berger. The drug has been under clinical test since 1958 by Drs. John P. Utz and Vincent T. Andriole, NIAID Laboratory of Clinical Investigation. Results of their study of patients hospitalized at the clinical center with a variety of culturally confirmed fungal infections were presented at the recent meeting of the American Thoracic Society.

Four of five patients treated with X–5079C showed dramatic clinical recovery from severe disseminated histoplasmosis. The one failure was questionable since treatment duration was considered too brief for valid evaluation. Three other cases of chronic cavitary histoplasmosis were effectively treated; cultures became negative in these patients. The drug produced some interference with liver function, but no irreversible damage, so far as present data indicate.

Of six patients who had blastomycosis, including two with osteomyelitis, four apparently made complete recoveries. Two of three patients with sporotrichosis infection severe enough to involve bones and joints were judged cured by treatment with X–5079C. They had shown no response to previous iodide therapy.

More study will be necessary to determine the true measure of the drug's effectiveness against aspergillosis. In a patient with the disseminated disease, marked clinical improvement occurred. Cultures became negative during treatment, but reverted to positive about 2 months after therapy. Two patients with pulmonary aspergillosis were treated. In one of these, cultures reverted to positive 7 weeks post-therapy, but in the other they remained negative as a result of treatment.

Patients with coccidioidomycosis failed to respond to the drug. However, earlier studies by Dr. Emmons demonstrate its activity against experimental coccidioidomycosis of mice. In the human drug trials, treatment was ineffective in cryptococcosis and candidiasis.

The new antibiotic, not yet commercially available, has demonstrated its usefulness in the treatment of human histoplasmosis, blastomycosis, sporotrichosis, and aspergillosis. There is some experimental evidence that its therapeutic spectrum is wider than may be inferred from these initial studies in patients.

Human serum inhibits growth of fungi

Potent components of normal adult serum markedly retard the in vitro growth and reproduction of the pathogenic fungus, *C. albicans*. Highly active at serum concentrations as low as 5 to 10 percent, the substance does not conform to the classical concept of an antibody. The results of this study are reported in the Journal of Investigative Dermatology by Drs. F. J. Roth, Jr., and M. I. Goldstein of the departments of dermatology and microbiology, University of Miami School of Medicine, Florida.

The investigators have tested over 250 individual sera from normal adults, as well as specimens from a variety of experimental animals. All sera inhibited fungal growth under conditions which permitted excellent growth when serum was absent. Other species of this genus of the fungi associated with man were also tested; these were even more strongly inhibited.

Increased incidence and population of *C. albicans* in the gastrointestinal tract and occasional candidiasis concomitant with antibiotic therapy are well-recognized phenomena. To determine whether the tetracyclines had an effect on the anti-Candida activity of serum, Drs. Roth and Goldstein administered 1 gram per day of chlortetracycline and tetracycline orally to 5 normal adult males for 12 days. Sera obtained during and after drug administration failed to show any significant decrease in ability to inhibit the in vitro growth of *C. albicans*.

To test the relationship of candidiasis and blood dyscrasias, the authors evaluated 51 sera from subjects with a variety of abnormalities, including patients with leukemias, multiple myeloma, Hodgkin's disease and aplastic anemia. Reduced inhibitory capacity was demonstrable in the cases of acute leukemia, Hodgkin's disease and multiple myeloma.

In distinct contrast to the blood dyscrasias, there was normal inhibition of Candida, without exception, in 33 patients with carcinomas of various organ systems. Even terminal status, X-ray or drug therapy did not appreciably reduce the inhibitory level of the serum. Average inhibitory serum activity was 80.3 percent for the 33 sera tested at a concentration of 20 percent. This contrasted to 81.8 percent for 68 normal sera tested. Average inhibitory value of this serum dilution in 10 patients with acute leukemia was 19.7 percent; in 7 with multiple myeloma, 13.2 percent.

Histoplasmosis fungus isolated in Washington, D.C.

The first isolation from soil in Washington, D.C., of the causative agent of histoplasmosis is described by a National Institute of Allergy and Infectious Diseases scientist in the July issue of Public Health Reports. The fungus was recovered from soil contaminated by starling excreta in two downtown parks. All 10 soil specimens taken from 1 park and 1 out of 5 specimens from the other park contained the causative agent.

The author of the report, Dr. Chester W. Emmons, Chief of the Medical Mycology Section of the Institute, points out that this serious fungal disease is generally believed to be prevalent only in rural environments. It has been assumed by many investigators that soil suitable for growth of the fungus which causes histoplasmosis could be found only in rural or small village environments, although the disease is already well documented as an important medical problem in areas surrounding Washington. In certain Maryland-Virginia communities up to 83 percent of the population have shown evidence of past exposure to histoplasmosis.

Past findings by Dr. Emmons and other scientists indicate that droppings from some species of wild birds as well as from domestic fowl create a soil site highly suitable for the growth of the fungus. Referring to the site of his latest findings, Dr. Emmons points out that "the park had been periodically and recently cleaned and there was no obvious contamination with bird excreta, although it is known that the soil under the sycamore trees where the collections were made is regularly contaminated with such material. It is obvious that roosting starlings can create a soil environment suitable for the growth of *Histoplasma capsulatum* even though bird excreta does not accumulate and remain on the surface of the soil."

MONDAY, FEBRUARY 19, 1962.

NEUROLOGY AND BLINDNESS ACTIVITIES

WITNESSES

DR. RICHARD MASLAND, DIRECTOR, NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS

DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

JAMES F. KELLY, DEPARTMENT BUDGET OFFICER

Object classification

[In thousands of dollars]

	1961 actual	1962 estimate	1963 estimate
11 Personnel compensation:			
Permanent positions	2,695	3,683	4,360
Positions other than permanent	188	254	298
Other personnel compensation	67	68	72
Total personnel compensation	2,950	4,004	4,730
12 Personnel benefits	257	339	384
21 Travel and transportation of persons	227	358	413
22 Transportation of things	40	47	49
23 Rent, communications, and utilities	98	135	136
24 Printing and reproduction	32	25	29
25 Other services	634	2,236	2,945
Payment to "National Institutes of Health management fund"	3,210	4,170	4,495
26 Supplies and materials	409	606	702
31 Equipment	419	704	419
41 Grants, subsidies, and contributions	39,983	49,614	56,909
Subtotal	48,258	62,239	71,212
Deduct quarters and subsistence charges	6	6	6
Total obligations	48,252	62,233	71,206

Personnel summary

	1961 actual	1962 estimate	1963 estimate
Total number of permanent positions	548	651	775
Full-time equivalent of other positions	30	39	45
Average number of all employees	450	605	732
Number of employees at end of year	516	716	831
Average GS grade	6.8	7.0	6.9
Average GS salary	$6,184	$6,282	$6,183

Program and financing

[In thousands of dollars]

	1961 actual	1962 estimate	1963 estimate
Program by activities:			
1. Grants and related contracts:			
(*a*) Research	30,865	39,126	46,421
(*b*) Fellowships	669	1,723	1,723
(*c*) Training	8,450	8,765	8,765
Total, grants and related contracts	39,983	49,614	56,909
2. Direct operations:			
(*a*) Research	5,040	6,425	6,566
(*b*) Collaborative studies	1,849	2,866	3,496
(*c*) Training activities	50	48	50
(*d*) Professional and technical assistance		1,500	2,300
(*e*) Review and approval of grants	1,019	1,343	1,499
(*f*) Administration	282	348	386
Total, direct operations	8,240	12,530	14,297
Total program costs [1]	48,223	62,144	71,206
Change in selected resources [2]	29	89	
Total obligations	48,252	62,233	71,206
Financing:			
Comparative transfers to other accounts	96		
Unobligated balance lapsing	1,252	8,512	
New obligational authority	49,600	70,745	71,206
New obligational authority:			
Appropriation	56,600	70,812	71,206
Transferred to—			
"Construction of Mental Health-Neurology Research Facility" (42 U.S.C. 292)	−7,000		
"Operating expenses, Public Buildings Service," General Services Administration (75 Stat. 353)		−67	
Appropriation (adjusted)	49,600	70,745	71,206

[1] Includes capital outlay as follows: 1961, $280,000; 1962, $472,000; 1963, $419,000.

[2] Selected resources as of June 30 are as follows: 1960, $196,000; (1961 adjustment, $56,000); 1961, $281,000; 1962, $370,000; 1963, $370,000.

Mr. FOGARTY. We are pleased to have you with us, Dr. Masland. You may proceed.

GENERAL STATEMENT

Dr. MASLAND. I have a statement which I wish to submit.

Mr. FOGARTY. We will be glad to place that in the record.

(Dr. Masland's statement follows:)

SUMMARY BY DIRECTOR, NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS, PUBLIC HEALTH SERVICE

Mr. Chairman and members of the committee, research advances in the prevention and cure of neurological and sensory disorders climax a decade of progress by this Institute, which, in November 1961, celebrated its 10th anniversary. Refinements in instrumentation and techniques helped further laboratory research and clinical investigation in a broad spectrum of disease categories. Studies in therapeutic procedures and understanding of the causes of various disorders are enhancing the possibilities for cure, relief, or prevention of some chronic ailments.

Techniques for identifying chromosomal abnormalities are yielding additional information on the possible genetic origin of mental retardation and other neurological disorders. These techniques, combined with better understanding of the mechanics of genetic transmission, are rapidly opening new research avenues.

Significant clinical results have been reported in the prevention of brain damage in premature babies by intravenous injection of glucose and sodium bicarbonate. A simplified and more rapid test has been devised to detect phenylketonuria (PKU), a form of mental retardation due to an inborn error of metabolism.

In other areas, surgical procedures for Parkinsonism are expected to be greatly aided by new techniques for objectively monitoring tremor and rigidity. The possibility of restoring lost myelin, the primary problem in multiple sclerosis, has been encouraged by preliminary animal experiments. Increased evidence suggesting that myasthenia gravis may have an immunologic basis has been reported. In glaucoma, a better understanding of the role of blood volume in increasing intraocular pressure may hasten our understanding of the cause of this blinding disorder.

Prospects for preventing certain cerebrovascular diseases have been heightened by a new anticoagulant that is particularly effective against the earliest phases of coagulation. Hope for the possible prevention of migraine headache is greatly increased by a new drug expected to become generally available this year.

The Institute's Laboratory of Perinatal Physiology in Puerto Rico, which is receiving increasing attention in this hemisphere, is highlighting the interest in international research. Also, investigators in other parts of the world are pursuing major studies, with Institute funds, which may widen frontiers of medical knowledge.

CONCLUSION

In conclusion, Mr. Chairman, the request for the National Institute of Neurological Diseases and Blindness for 1963 is $71,206,000 as compared with the $62,233,000 available in 1962. The request for 1963 will provide for an increase of $7,295,000 in research grants; an increase of $111,000 in direct research for expansion of the current programs and for the establishment of satellite operations; an increase of $575,000 in collaborative studies for expansion of the collaborative project in cerebral palsy and mental retardation, and other collaborative programs including biometry and epidemiology; an increase of $800,000 in professional and technical assistance for further expansion of programs initiated in 1962; an increase of $156,000 in review and approval for professional and clerical staff engaged in processing, analyzing and managing the grants and awards, and an increase of $36,000 for overall planning, direction and coordination of the programs of this Institute.

Statement by Director, National Institute of Neurological Diseases and Blindness, Public Health Service, on "Neurology and Blindness Activities"

Mr. Chairman and members of the committee, it is a pleasure to appear before this committee to review with you the research and training developments of the past year directed toward the prevention and cure of neurological and sensory disorders.

As the youngest of the seven Institutes, it was our pleasure to celebrate our 10th anniversary recently and to review scientific accomplishments. Research advances in general come very slowly, but viewed over a decade the progress is indeed significant. A review of these advances provided an opportunity to understand how dependent each step of progress during 1961 has been upon the many accomplishments which have preceded it.

Among the accomplishments of this past decade which have provided a base for research advances of the past year are such instrumentation and techniques as the electron microscope, isotope tracers, X-ray diffraction, tissue culture, labeled antibodies with fluoroescence, autoradiography, microelectrodes, paper chromatography and amino acid analyzers, the electroretinogram, and computers.

During this past year, tissue culture has advanced our knowledge of chromosomes, labeled antibodies have increased our knowledge of immunology and have provided important information relative to multiple sclerosis, isotope tracers have advanced our understanding of cell division in the cornea. Paper chromatography and amino acid analyzers have improved diagnostic measures of inborn errors of metabolism. The electroretinograph has aided in the diagnosis of visual disorders; X-ray diffraction has made possible important advances in the understanding of genetics; and microelectrodes have been important in the study of the subcellular areas of the brain. Autoradiography has given us a powerful new tool for the study of the regeneration of the central nervous system; the electron microscope has made possible great strides in understanding the finer structures of tissues; and various types of computers are providing methods for studying problems which involve multiple factors.

PROGRAM PROJECT GRANTS

Neurological research is dependent, to a large extent, on long-term projects requiring the use of complex equipment and a variety of technical skills. As a part of the overall program of broad grants at the National Institutes of Health, this Institute is now supporting 11 program project grants at medical institutions.

The Institute's program project grants involve either a multidisciplinary attack on specific neurological or sensory diseases or a disciplinary attack on a group of neurological and sensory disorders. Three centers have been established for neurosensory disorders of vision, hearing, and equilibrium; three for cerebrovascular research; two as neurological clinical research centers; and one each for epilepsy, brain damage, and for a broad neurophysiological study of various neurological diseases.

TRAINING

The training program of the Institute is now in its 10th year. Since completion of training for clinical neurology, ophthalmology, and otolaryngology requires a minimum of 5 years after internship, the impact of these programs is just beginning. However, it was believed desirable at this time to review the status of the training program, consider its objectives, and evaluate the extent to which the present methods of support and program development are actually achieving the desired results. Therefore, Institute staff members met with program directors and other specialists in each of the fields of training, and prepared a detailed program analysis of training.

To date, Institute training programs have been directed entirely toward training for teaching and research, as opposed to practice. Thus, in the clinical neurology training programs, 67 percent of those completing training have remained in the fields of teaching and research. The number of qualified neurologists has now increased from 250 in 1951 to 818 in 1961.

It is evident that already a very significant proportion of the men now engaged in teaching and research in clinical neurology are individuals whose specialized research training was made possible by the Institute's training program. Similar findings are revealed in respect to ophthalmology, otolaryngology and the basic neurological sciences, although these programs have been in progress for too short a time to have produced an equivalent impact.

NEUROLOGICAL DISORDERS OF INFANCY AND CHILDHOOD

A major program of this Institute is the large area of neurological disorders of infancy and childhood. These disorders include cerebral palsy, mental retardation, congenital malformations of the nervous system, and congenital blindness and deafness. As a group they afflict more than 6 million Americans, many of whom have been seriously disabled throughout their entire lives. In addition, another quarter of a million babies are born each year with these disabilities.

To meet this challenge, the Institute is currently spending more than $11 million a year in an attempt to increase knowledge of the causes, prevention, and treatment of these disorders.

Central to the Institute's research in this area is the collaborative perinatal research project. This long-term venture in medical research will involve 50,000 expectant mothers and babies and 15 hospital teams. To date, 23,000 mothers and 17,000 children have been studied and detailed records sent to the central office for statistical analysis.

The project has already produced useful preliminary data and has given us a number of worthwhile byproducts. For example, this year, a study of 7,500 pregnancies in our collaborative project has linked prematurity to smoking during pregnancy. Prematurity, which has long been recognized as an important factor in perinatal problems, is usually defined in terms of birth weight. In this study, birth weight decreased proportionately to the number of cigarettes smoked daily during pregnancy. This result confirms earlier reports on the effects of smoking on birth weight.

During the last few years, we have learned much more about the biochemical aspects of chromosomal disturbances. Numerous abnormalities—which represent deviations in both number and structure of chromosomes—are being observed. For example, this year an abnormality associated with mental retardation and with a striking feature of failure of speech development has been correlated with chromosome abnormality. Similarly, abnormalities have been reported in relation to cerebral palsy and to the simultaneous occurrence of leukemia and Mongolism. Although the causes of these abnormalities are not yet understood, this is believed to be a most promising area of research.

Over a long period of time, asphyxia has been recognized as a factor in brain damage. It is imperative, therefore, that we know much more about when, how, and why asphyxia occurs. Various current research studies are teaching us much more about the environment of the baby before birth and during the birth process. From such knowledge, we hope to understand more about the factors involved in prenatal and natal asphyxia.

It has been reported by some scientists that when an oxygen deficiency occurs after normal breathing has been established, the brain damage is especially severe. In an effort to predict respiratory distress in the newborn, a miniature recording instrument called a plethysmograph is now being used to study the sequence of events during the first hours and days of life.

Another step in prevention of brain damage resulting from breathing difficulty in premature babies in the intravenous injection of glucose and sodium bicarbonate. The ramifications of this technique are being explored further in Institute studies in our perinatal laboratories in Puerto Rico. Meanwhile, within one hospital, preliminary clinical trials indicate a very significant decrease in neonatal mortality during a 1-year trial of this new method of management.

Much progress has been made in the detection of inborn errors of metabolism. The early detection of phenylketonuria, for example, has been extremely important to the treatment of this disorder by diet. A new, inexpensive test has been developed by Institute grantees which can detect this disorder within a few days after birth. This test, based on a bacterial inhibition principle, uses only a drop of blood blotted on a filter paper to detect phenylketonuria.

PERINATAL PHYSIOLOGY IN PUERTO RICO

Until the establishment of the Laboratory of Perinatal Physiology in Puerto Rico, few animal studies had been conducted on neurological disorders which stem from adverse perinatal factors. Few laboratory animals possess pregnancy physiology sufficiently comparable to man to be useful for research. However, the monkey *Macaca mulatta*, studied in Puerto Rico, is an ideal subject because of its physiological similarity to man.

Among advancements in our knowledge resulting from studies in this Laboratory has been the establishment of consistent clinical patterns of mental retardation and physical handicaps resulting from asphyxia during birth. It now seems possible to mitigate the severity of the deficits induced under conditions of asphyxia by the administration of sodium carbonate and glucose during birth.

The possibility that abnormally strong uterine contractions during labor may predispose to cerebral hemorrhage will soon be explored in collaboration with others. The possibility that the cerebral hemorrhage signals a condition in which blood is forced from the contracting arteries into a weakened capillary bed is being entertained.

The role of hyperbilirubinemia in kernicterus can now be studied more thoroughly since for the first time a condition, comparable to that in human kernicterus, has been produced in an experimental animal.

The unique research opportunities this facility affords have drawn the interest of a great many scientists from other countries, especially from Central and South America, who have joined in the research efforts. Thus it is rapidly becoming an important research center of particular acclaim in this hemisphere.

EPILEPSY

In studies of the genetics of convulsive disorders, preliminary data provide evidence of a hereditary factor in seizures. It may be possible, on the basis of clinical and electroencephalographic criteria, to delineate specific genetic subgroups with the various epilepsies. In pursuing these studies further, grantees concluded that the centrencephalic type of electroencephalogram is the expression of a form of epilepsy in which there is a significant genetic factor. In this group, investigators found a gradual increase of seizures with a peak frequency of convulsions occurring between the ages of 4½ and 16½ years and a gradual decline to almost no seizures after 40.

In another 10-year followup study of children with epilepsy, a grantee reported that preliminary results indicate that social adjustment is important to the prognosis of the disorder. The investigators also found that intelligence appeared to have some relationship to the capacity for social adjustment.

This year encouraging reports have been made regarding the use of a new anticonvulsant in children with certain types of epilepsy previously resistant to drug therapy. A preliminary report concerning the new drug, R–594, indicates that complete control of seizures was found in 31 percent of a group of patients who had not responded to other medication, and a 75-percent reduction of seizures was reported in 32-percent of the cases. A 50-percent reduction of seizures was reported in another 9-percent.

Still another anticonvulsant, ethosuximide, has been tested in petit mal epilepsy and found to control seizures, with only minor side effects, in approximately 63 percent of patients.

A closer look at the effectiveness of the numerous drugs available for treatment of epilepsy has indicated that there apparently is a specificity of drug effectiveness for different individuals. Investigators are working toward better evaluations of drug therapy so that the most effective drug can be prededuced for each individual. Toward this end, an Institute grant is making possible a broad evaluation of drug therapy for epilepsy.

HEADACHE

Headache is a vast economic problem as well as a confusing medical one. It afflicts large numbers of persons and interferes with productivity. Several investigators have conducted careful double-blind studies of a new drug, methyl lysergic acid butanolamide, and its effect on migraine patients. The drug is a helpful tool in investigation of the mechanisms of headache. Investigators are convinced that it aids in the preventation of migraine when taken between attacks. This new medicine is expected to be generally available to physicians some time during 1962.

Information from findings by grantees showed that persons subject to migraine headaches had about twice the incidence of abnormal brain wave patterns as patients without migraine. These findings have encouraged investigators to treat migraine patients who have abnormal EEG's with anticonvulsants. The reported results have been favorable in 80 percent of a highly selected group of cases.

As a continuation of effort which started during a grant-supported symposium on evaluation of drug therapy in 1960, the panel on headache completed its classification of headache in 1961. Upon this classification a national comparison of effectiveness of headache remedies can be based with improved validity.

PARKINSONISM

Within recent years, efforts have been directed toward the control of Parkinsonism by drug and surgical techniques. Not long ago a grantee demonstrated how muscular rigidity can be relaxed and tremor reduced by the application of chemicals to a certain nucleus located deep within the brain. These techniques, called chemothallidectomy and chemopallidectomy, relieve the symptoms but do not halt the progress of the relentlessly progressive disease.

The current medicinal treatment for Parkinsonism embraces a wide assortment of synthetic drugs that are more specific in action and less disturbing to the patients than those used a decade ago. Nevertheless, we still are not able to arrest the disorder, but merely to relieve certain symptoms. It is imperative that we not only search for new drugs for therapy, but that we find reliable means for evaluating the many drugs now available. In the current Institute evaluation of drug therapy, the involuntary movement disorders, such as Parkinsonism, are receiving considerable attention. The probability of obtaining more effective drugs will be increased by further elucidation of their mode of action.

As a part of a broad study to devise objective measurement of abnormal clinical conditions in Parkinsonism, grantees have developed objective techniques for monitoring and graphically tracing tremor and for measuring muscular rigidity. These techniques used during surgery help the surgeon determine, moment by moment, how the tremor of the Parkinson patient is affected by surgery. Graphic tracings, if correlated with patient improvement, may constitute a useful diagnostic pattern. Measurements of muscular rigidity may also prove helpful in evaluating the effects of brain surgery in Parkinsonism.

SPEECH AND HEARING

Problems of speech and hearing continue to be among the most common causes of disability. Although certain forms of deafness, especially those which result from infection of the middle ear in infancy and childhood, are rapidly being eliminated, there is evidence that the increased survival rate of children experiencing asphyxia or birth injury in the neonatal period may lead to an increased total number of deaf individuals.

Significant research advances are being made regarding hearing loss in childhood. The use of antibiotics has materially reduced the incidence of hearing loss caused by infection. Recently it has been discovered that many cases of congenital deafness have actually been a result of neonatal asphyxia or jaundice. Improved obstetrical and pediatric practices are greatly reducing the frequency of these complications. With children unable to talk, refined diagnostic procedures are defining with increasing accuracy the exact nature of the defect. They also are permitting the development of more effective methods for remedial and educational methods of compensation. Among the older age groups, about 20 percent are suffering from otosclerosis, or which possibly one-half may be improved by surgical restoration.

During the past year, the Institute has considered methods for an intensification of the attack on hearing disabilities and the general problem of communication defects. A group of special consultants has recommended that interdisciplinary centers concerned with research and research training should be developed, and proposals for four such major medical centers are now pending.

This year the Institute has also supported symposia to encourage the exchange of information and new knowledge and to stimulate greater interest in this general field of research. Among these have been the following: "Sensory Mechanisms," Salt Lake City, Utah; "Research in Hearing and Speech Pathology in the South," Atlanta, Ga.; "Cerebral Dominance," Johns Hopkins Hospital, Baltimore; "Research in Potential in Voice Physiology," Syracuse University, New York; "Conference on Codification of Communication Disorders," New York City, N.Y.; and "Ad Hoc Advisory Group for Speech and Hearing," Bethesda, Md.

CEREBROVASCULAR DISORDERS

Although we are now able to treat successfully some of the cerebrovascular disorders, certainly the most important aspect of this field is early diagnosis, and this aspect needs to be emphasized. In alerting physicians to the possibility of cerebrovascular disease in patients, it is valuable to know the conditions with which such disorders are commonly associated and to know that some people are more susceptible to these disorders than others.

In the past, various causes have been suggested for atherosclerosis. This year many of these factors were reexamined by an Institute grantee. Mechanical stress, such as hypertension was again implicated, as was diabetes, with the latter apparently serving to accelerate the condition. Contrary to previous beliefs, age was considered only an accompanying factor. Also, most nutritional aspects and sex differences were ruled out as causative factors, although they may accentuate the problem.

Nevertheless, other studies of dietary habits suggest a relationship between the amount and type of food consumed and the incidence of arterial disease. While there is yet no final proof that strokes can be prevented by dietary control, the reduction in blood cholesterol by dietary means, which also emphasize weight control, may lessen the development or extension of atherosclerosis and hence the risk of strokes.

In the course of diagnosis, in many cases it is particularly important for therapeutic purposes to determine the exact site of the diseased blood vessel. Improvements in angiography, EEG, oscillometry, and other diagnostic techniques hold promise for achieving this goal.

An Institute cooperative study, important to the treatment of cerebrovascular diseases, is nearing completion. The Institute's cooperative study of intracranial aneurysms and subarachnoid hemorrhages, was begun in early 1958. In addition to the analysis of subarachnoid hemorrhages and aneurysms, the study may also prove helpful, through its large reservoir of clinical data, in solving the general problems of cerebrovascular disease.

The Institute's cooperative anticoagulant project, begun in 1957, is in the final stages. This study has indicated that the use of anticoagulant drugs in preventing little strokes, in warding off the occurrence or reoccurrence of major attacks, and in reducing the neurological deficit that may result, is feasible but may involve definite risks and problems.

Recently a new anticoagulant was developed that may avoid some of the difficulties associated with such anticoagulants as heparin or dicumarol. Animal studies of this substance, thromboplastinase, have shown that it strikes selectively at the earliest phases of coagulation. Clinical studies are now being conducted.

A precise knowledge of the role of anticoagulants may require a more accurate understanding of the clotting mechanism. Pathological examination of diseased cerebral arteries is revealing the existence of arteriosclerotic plaques and of small neural thrombi. The recurrent formation and subsequent release of many such thrombi, or clots, may account for recurrent minor vascular attacks, and loss of consciousness, in some patients.

NEUROMUSCULAR DISORDERS

In the Institute's neuromuscular program, a systematic effort has been made to distinguish and classify muscular and neuromuscular disorders. A more accurate classification is essential to research in this area. Advances this year in the analyses of muscle biopsy, determination of abnormal protein elements in muscle, and demonstrations of other enzymatic and chemical disturbances have aided in making the differentiation of neuromuscular disorders more effective.

Developments in the field of immunology, especially in regard to autoimmune diseases, have had an impact on neuromuscular research. Earlier predictions that myasthenia gravis might be an autoimmune disease have received preliminary substantiation. Grantees have determined that a constituent of serum from myasthenic patients varies in concentration in relation to the severity of the symptoms. The constituent, called serum complement, is involved in immune reactions of the blood. An abnormal globulin constituent from myasthenic patients binds to the serum complement as well as to muscle fibers. These results lend support to the hypothesis that the cause of myasthenia gravis may be based on an autoimmune reaction.

MULTIPLE SCLEROSIS

This year has seen further progress in our study of certain conditions which appear to bear a significant relationship to multiple sclerosis. There has been a clarification of the nature of the autoimmune process, "allergic encephalomyelitis," an experimental disease of animals. It differs from the human disease in that it represents a single, acute episode which may progress to either death or recovery, whereas multiple sclerosis is a recurrent and remittent type of disease.

A process resembling allergic encephalomyelitis has recently been reproduced in tissue culture. Treatment of the tissue culture with serum from an animal suffering with allergic encephalomyelitis produces liquefaction of the myelin substances of the nerve sheath in tissue culture. It is significant that this year it has also been demonstrated that blood serum removed from patients suffering from acute episodes of multiple sclerosis is capable of producing liquefaction of the nerve sheath in tissue culture.

As previously reported, considerable attention is being given by grantees and other scientists to the study of other animal diseases bearing resemblance to multiple sclerosis. The possibility of a virus causation of some of these animal diseases has heightened interest in further search for a virus in multiple sclerosis. Plans have been developed this year for the establishment of research centers where efforts may be made to isolate viruses from patients with multiple sclerosis and other chronic disorders of the nervous system.

The destruction of myelin is the primary characteristic of multiple sclerosis. In recent years we have learned more about the structure and chemistry of myelin. Also, we have been able to identify many differences between peripheral and central nervous system myelin. Investigators in the past have found that regeneration of myelin is possible in the peripheral nervous system. This year we are encouraged by grantee studies which demonstrate for the first time myelin regeneration in the central nervous system in mammalian animals.

DISORDERS OF VISION

One of the leading problems in eye disorders is increased pressure within the eye which leads to glaucoma. For a number of years, scientists have attempted to find the mechanism which elevates this pressure. Recent findings indicate that intraocular pressure is due in part to variations in the amount of blood retained within the blood vessels of the eye, especially in the ciliary processes. Blood volume has been studied by observing the effects of the drug, acetazolamide, which is administered to patients to lower the intraocular pressure. It was noted that this drug acts by constricting the blood vessels of the eye. Constriction has been further localized in the arterial vessels of the iris which feed the ciliary processes directly and could regulate the blood volume of this area.

Institute biochemical and morphological studies are yielding new information on the basic components of the tissues of the eye. A new enzyme, sodium-potassium activated adenosine triphosphatase, has been found to play an important role in the formation of aqueous humor, which in turn affects the internal pressure of the eye.

Much of the effort in the field of ophthalmology is directed toward a greater understanding of the essential make-up and function of the visual receptor cells in the retina. Electronic computer techniques have widened the scope of the ERG (electrical recordings of the eye's response to light) as a clinical tool. By means of these techniques, Institute investigators and other scientists have been able to record ERG's where there was no response by conventional recording methods. Institute investigators have also been able to detect a difference in response depending on the part of retina stimulated. This finding will aid in determining the part of the retina affected by disease or degeneration.

Proceedings of an Institute-supported Conference on Diabetic Retinopathy have now been published. Conclusions indicate that a careful control of diabetes may delay the onset or minimize the severity of diabetic retinopathy. This vascular disease is becoming more common as a complication of the prolonged life of the diabetic.

With Institute support, much progress has been made during the last 5 years on the preservation of corneas for corneal transplants. In addition to preservation by dehydration, recent grantee studies indicate that corneas may also be stored and shipped in the deep frozen state. Since freezing is a simpler process, it makes possible the storage of donor material until needed.

Studies of disease processes and regeneration in the cornea are facilitated by knowledge of the cellular activity of this tissue. Improved autoradiographic techniques make it possible to incorporate a radioactive substance in the cell nuclei before the cell divides and then to trace the course of the cells and their divisions in the growth process.

A new technique for exercising and retraining the macula of the eye with a red light may prove useful for the treatment of amblyopia. Referred to as pleoptics, the new technique may restore binocular vision to persons whose sight in one eye has been dimmed through disuse.

A workshop to develop a definition of blindness has been formed to serve the varied needs of the different agencies serving the blind. Participating are various professional and social workers, statisticians, Bureau of State Services representatives, and Institute personnel. They are urging better means of evaluating the true status of the patient's vision and of coordinating visual efficiency with visual acuity.

In conclusion, Mr. Chairman, the request for 1963 is $71,206,000, which provides for increases in grants for about 220 additional research projects as well as increases in direct operations. It is distributed among program activities as follows:

Grants and related contracts:	
Research	$46,421,000
Fellowships	1,723,000
Training	8,765,000
Subtotal, grants	56,909,000
Direct operations:	
Research	6,566,000
Collaborative studies	3,496,000
Training activities	50,000
Professional and technical assistance	2,300,000
Review and approval of grants	1,499,000
Administration	386,000
Subtotal, direct operations	14,297,000
Total 1963 appropriation request	71,206,000

Dr. MASLAND. The year 1961 marked the 10th anniversary of the establishment of the National Institute of Neurological Diseases and Blindness. This anniversary provided an opportunity for a review of neurological and sensory research developments during the past decade. The record of advances was a most impressive one.

RETROLENTAL FIBROPLASIA

Heading the list is the conquest of retrolental fibroplasia. The Institute's collaborative study of oxygen concentration as a cause of this disorder in prematures has saved the sight of many hundreds, perhaps thousands.

Mr. FOGARTY. Was some of this work done in England?

Dr. MASLAND. Some was. The Institute's contribution was establishing very rapidly without question, the relevance of this factor in human populations.

Mr. FOGARTY. The Institute on Neurological Diseases really developed this?

Dr. MASLAND. And established without question its relevance to clinical medicine.

This discovery has saved the Nation about a half billion dollars aside from the saving of sight which was involved.

Mr. FOGARTY. I thought it amounted to more than that.

Dr. MASLAND. This is an absolute minimum in terms of the cost of taking care of these people.

Mr. FOGARTY. That is what I meant. And they live a normal life.

DISEASES OF THE EYE

Dr. MASLAND. That is right. In glaucoma important advances have been made in diagnosis through tonometric examinations. When this disorder is diagnosed early the use of new drugs is preserving vision in a large percentage of cases.

In our enthusiasm for basic research, we often fail to emphasize certain clinical advances which, though less spectacular, are bringing direct help to the patient. Advances in operation for cataract are facilitating clean removal of the lens in children as well as adults, and in the early stages of hardening of the lens.

The development of corneal transplantation is restoring sight to many with scarred corneas and new means of preservation of corneas is now available. They are also experimenting with plastic cornea so we may not have to use donor eyes for this purpose.

A new method of treatment called pleoptics appears promising for a type of partial blindness in one eye which afflicts 2 percent of the population. This treatment is based on the proper stimulation of the inactive eye.

Mr. Fogarty. We shall place your special statement on eye disease activities in the record at this point.

(The statement follows:)

Special Report: Disorders of Vision

THE PROBLEM

Over half of the estimated blind population of 350,000 in the United States are persons over 40. In a large percentage of these cases, blindness could have been prevented. In this older group, early recognition and treatment of glaucoma will prevent many cases of blindness. Cataract surgery will restore sight to many others. In spite of these great advances in treatment, the means to prevent either cataract or glaucoma is still lacking. Nor do we know how to stem the course of diabetic retinopathy, another disorder which becomes more prevalent with increasing age. Other important ocular disorders are the infectious diseases, injuries and poisoning, and vascular disorders.

In terms of care, blindness costs the country over a billion dollars a year, but this is not the whole story. An estimated 3,680,000 workdays a year are lost by the blind and partially blind.

ADVANCES

Glaucoma

Glaucoma, the second ranking cause of blindness in the United States is responsible for one out of every eight cases of blindness. It is an insidious and progressive disorder associated with an increase in the pressure of fluids within the eye which can lead to marked reduction in vision or even total blindness. Screening programs in many communities reflect a growing awareness of the importance of early detection of glaucoma. Through these programs, increased intraocular tension—a frequent precursor of glaucoma—has been found to be present in 2 percent of all persons over age 40, and the sight of many has already been saved through early detection.

A 5-year Institute cooperative study with the Bureau of State Services is seeking more effective methods for diagnosing glaucoma. Now in its third year, this committee has developed a protocol and standardization of tests. Using these tests, a number of individuals will be examined and the course of their disorder observed in order to evaluate the validity of diagnostic techniques.

Over the past few years, a number of Institute studies have been directed toward a better understanding of the mechanism by which the pressure within the eye is elevated. Refined techniques enable investigators, for the first time, to carry out pressure measurements in the small blood vessels of the eye. Results will help clarify the obscure relation between changes in vascular pressure, aqueous tumor dynamics, and intraocular pressure regulation. Recent findings indicate that the pressure is due in part to the ocular blood volume, especially in the ciliary processes. Investigators have noted that acetabolamide lowers the intraocular pressure by constricting the blood vessels of the eye. Further studies localized the constriction in the arterial vessels of the iris. These arterial vessels feed the ciliary processes directly and thus could regulate the blood volume.

Other studies center around a better understanding of the function of enzymes and other basic components of the tissues of the eye. An investigation of the distribution of a new enzyme, an ATP-ase, in eye and brain tissues led to the conjecture that this enzyme is involved in the secretion of aqueous humor, which in turn affects the intraocular pressure.

Methods of evaluating drug therapy for glaucoma have been studied by a panel of experts which met as a part of an Institute-supported drug therapy symposium. The published report of the panel lists criteria for improving the evaluation of drugs and discusses techniques and methodology for determining and testing results.

Cataract

A new technique for removing congenital cataracts in children allows the opaque lens (cataract) to be drawn out by "needle aspiration" instead of breaking the fibers which hold the lens in place. Cataract surgery in children was previously very difficult because of the toughness of these fibers, which had to be broken in order to extract the lens. Adult surgery for cataracts is often facilitated by the enzyme, alphachymotripsin, which Institute and grantee studies have proved to be safe to use.

Several studies are underway at the Institute and elsewhere to investigate the effects on the lens of toxic agents, vitamin deficiencies, and radiation, and to observe the cellular and cytoplasmic changes which cause the lens to become opaque. A current Institute study includes the effects of cosmiclike radiation (cosmic ray primaries) on the mouse lens.

Uveitis

Uveitis, an inflammatory disease of the choroid, iris, or ciliry body, has long been a difficult research problem. Symptomatic treatment of uveitis with steroids is saving vision in many who previously would have been blinded by this disorder. Valuable information for the treatment of toxoplasmosis, one form of infection which can cause uveitis, has been obtained through a recent investigation with the electron microscope. This study of the life cycle and living conditions of the toxoplasma parasite led to its classification, for the first time, as a sporozoan.

Retina

A better understanding of the visual receptor cells of the retina, their structure and function, has been the objective of many research studies in eye disorders. Th electroretinogram (ERG), long a source of information on how the retinal cells respond to light stimulus, has recently become an even more valuable clinical tool through the use of electronic computer techniques. These new techniques have made it possible to record ERG's in cases where responses had not previously been detected by conventional recording methods. Institute investigators found the sensitivity of these ERG's to be related to the extent of the functioning retina as determined by visual field measurements (perimetry). Other studies by the same investigators found a difference in response to light stimulus depending on where the light falls on the retina. Lesions affecting the central vision, previously undetectable, can now be distinguished in an objective fashion by the ERG.

One Institute scientist has observed the appearance and increase in concentration of the pigment of the retina in the growing animal. These and other findings will be coordinated with biochemical, morphological and functional changes in the developing animal. For instance, concentration of rhodopsin (retinal pigment) has been found to parallel the sensitivity of the ERG.

Retrolental fibroplasia

It was estimated in 1952 that there were nearly 2,000 new cases of blindness each year from retrolental fibroplasia. Through a cooperative study supported by this Institute involving 18 hospitals, the cause of the disorder was clarified and preventive measures developed. A concerted effort was then made to place this knowledge in the hands of physicians, hospitals, and the general public. As a result, in a short period of time the disorder was practically eliminated and in 1958 it is estimated that only 28 cases occurred.

With a total expenditure of a little more than $50,000 by this Institute and two cooperating voluntary agencies, the final answer to retrolental fibroplasia was obtained. This was a small investment for the nearly 13,000 persons it is believed were saved from such blindness since 1954. The cost of care for these persons for an entire lifespan would have been about $784,095,000. The saving in lifetime support of the 1,860 cases which are prevented yearly amounts to approximately $120,900,000.

Diabetic retinopathy

Published proceedings of an Institute-supported conference on diabetic retinopathy brings together in one volume the opinions and comments of many experts on ways to avoid this retinal condition which develops as a complication of the prolonged life of the diabetic. Conferees agreed that a careful control of diabetes may delay the onset or minimize the severity of the vascular disease.

Cornea

For the past 5 years, the Institute has supported research relating to the preservation of corneas for transplants or graftings to replace opaque corneas of patients. Much progress has been made and corneas can now be preserved in storage for long periods. This has also made possible their international shipment. In addition to dehydration, recent grantee studies indicate that corneas may be satisfactorily preserved by deep freezing, a method which is much simpler than dehydration.

To better understand disease processes and regeneration in the cornea, the cellular activity of this tissue is under study. Improved autoradiographic techniques make it possible to inject a radioactive substance in the cell nuclei before the cell divides and to trace the course of the cells and their divisions in the growth process. Applied to eye tissue, investigators at other institutions have been able to make counts of cell populations in single cell layers of lens epithelium and corneal endothelium. Using the same methods, Institute investigators have made an extensive study of the cell cycle in the corneal endothelium. Later studies will do the same for the lens epithelium.

Specific cells in the cornea have been found important in the process of wound healing. At the junction of the sclera and cornea, these cells (called mast cells) form a barrier to the formation of blood vessels in the cornea. In injury involving this region, however, the barrier is broken, permitting the blood vessels to grow across the cornea. This formation of blood vessels makes the healing process more analagous to that in other parts of the body, and often leads to permanent opacities of the cornea.

Refractive errors

For the first time in 50 years, new theories are being offered to explain the fundamental mechanisms at fault in nearsightedness and other refractive errors. The findings are a result of a 3-year study which applied mathematical techniques to existing data on eye measurements. The analysis of correlations between the five optical elements (ocular refraction, axial length, chamber depth, corneal power, and lens power) of the human eye have led to two basic assumptions. One is that the inherent elasticity of the choroid coat of the eye may have importance in abnormalities of refraction. It helps to determine the final shape of the eye and counteracts part of the intraocular pressure. The second assumption is that movements of the ciliary muscle (which focuses the eye) are controlled by the brain. During the growth process, the ciliary muscle increases or decreases the axial length of the eye in an effort to develop perfect vision. The new theories have significance not only for possible therapy for developing refraction anomalies, but also for glaucoma, since the stretch of the choroid affects the intraocular pressure.

Amblyopia

A considerable segment of our population is affected by a form of reduced vision known as amblyopia. In this condition there is no apparent physical abnormality, but for some reason, the two eyes do not focus together to give the patient binocular vision. Either as a result or as a cause of this lack of binocular vision, one eye fails to develop fully in its function. If discovered in children, the disorder can be treated by covering the functioning eye and forcing the underdeveloped one to function. However, previously, if not corrected in the early developing years, there was no effective measure for correcting the condition in the adult. Recently, in Europe, scientists have become encouraged by a new technique of exercising and retraining the area of central vision in the retina. This may prove useful for the treatment of amblyopia in the adult, as well as other visual disorders. This new type of retraining is referred to as pleoptics and may become a field of interest and importance.

Definition of blindness

A workshop to develop a definition of blindness has been formed to serve the varied needs of the different agencies serving the blind. Participating are various professional and social workers, statisticans, Bureau of State Services representatives, and Institute personnel. They are urging better means of evaluating the true status of the patient's vision and of coordinating visual efficiency with visual acuity. Measurements of visual acuity do not always indicate how much useful vision the patient has.

Statistics on blindness

The emphatic need for more information of the incidence and prevalence of blindness has been recognized by the Institute in its model reporting area for blindness statistics. This program, now in the planning stages, will take advantage of the fact that at least 28 States have mandatory blindness registers. In cooperation with voluntary agencies and the Chronic Diseases Division of the Bureau of State Services, the Institute hopes to assist these States in developing uniform statistics on the registered blind, according to a standard definition, so that figures from the various States are comparable. The States would prepare statistics on the blind by age, sex, race, and visual acuity, as well as by etiology and the sight of the eye affected. The model reporting area could then pool and analyze the data from the member States in order to arrive at meaningful estimates of incidence, and possibly prevalence, of blindness for the entire United States. The model reporting area will also encourage and assist in studies of etiology, survivorship, and characteristics of the blind population.

SPEECH AND HEARING

Dr. Masland. The field of speech and hearing has also seen important advances. The control of infections of the ear in childhood has reduced the frequency of middle ear deafness. It is now possible to restore an eardrum destroyed by disease. Among adults, most dramatic has been the surgical restoration of hearing after years of deafness produced by otosclerosis.

Recent years have seen virtual elimination of gross cerebral palsy due to kernicterus.

The outlook for the epileptic has been greatly modified. Anticoagulants reduce recurrence rates in certain forms of strokes.

PHENYLKETONURIA

We have accomplished control of certain inborn errors of metabolism previously considered hopeless, for example, the dietary control of phenylketonuria. This year there has been developed a new screening test capable of diagnosing this disease within the first week of life. The test appears to be simple, practical and reliable——

Mr. Fogarty. This is something new? The last time you appeared you said it was 3 weeks?

Dr. Masland. Three months.

It has been demonstrated that the chemical appears in the blood 2 or 3 days after the baby is on a milk diet.

Mr. Fogarty. In effect, if this turns out to be so, this is the procedure which can be adopted in every hospital?

Dr. Masland. That is right, and before the baby goes home. The problem is that once the baby has left the hospital, it becomes many times more difficult to be certain of obtaining a specimen.

STANDARDS OF PATIENT CARE COMPARED WITH RESEARCH PROGRESS

In spite of these material advances which have been placed in the hands of the medical profession, in some areas the standards of patient care have not kept pace with medical progress. For example, some 800,000 persons in the United States could lose their sight because of lack of application of available diagnostic techniques for glaucoma.

Similarly, in epilepsy, many persons continue to have seizures needlessly because of lack of application of anticonvulsants. These demonstrate only two of the gap areas between research advances and patient care.

In order to close this gap, a new professional and technical assistance program has been established within the Bureau of State Services. One of its initial programs will be the development of a much broader glaucoma screening program. We are developing a model reporting area through which to monitor the impact of this and other forms of treatment.

Another program will be working with the Children's Bureau to evaluate the practicability of mass screening of newborns for phenylketonuria and hopefully to develop a better screening test which might detect a number of these abnormalities instead of just one on the basis of a single sample.

PROGRESS IN TRAINING PROGRAM

A review of the Institute's training program this year again attests to the value and effectiveness of this activity. Figures just released by the American Medical Association show that during the calendar year 1961 the number of neurologists in full-time teaching and research increased from 92 to 139.

In ophthalmology the number of teacher-investigators increased from 43 to 64 and in otolaryngology from 4 to 33. It is evident that the impact of these programs is now beginning to make itself apparent as our trainees complete their programs which often require 6 to 8 years.

You have heard in earlier testimony a beautiful example of the impact of our clinical research training program. I think some question was raised as to the real contribution that clinical research training is making to research.

There has been earlier discussion of the treatment of winter pinkeye. This is an example of the interaction of basic and applied research. The chemicals were developed in the Cancer Institute for control of cancer. The investigator who applied them to the eye is a man who was one of our former clinical associates. He was trained under an ophthalmology training grant at the Massachusetts Eye and Ear Infirmary and did his initial work there.

He has been supported by this institute in his research for 3 years. As a result of this preliminary training, he was able to discover the applicability of this chemical to the treatment of a human eye disease.

I think without any question the people whose vision is saved as a result of this discovery owe it to the foresight of this committee in establishing these important training programs 5, 6, and 7 years ago. This is a very clear-cut example of the direct impact of this training.

SUMMARY OF BUDGET FOR 1963

In conclusion, Mr. Chairman, requests of this Institute for 1963 are $71,206,000 as compared with $62,233,000 available in 1962. This request will provide for an increase of $7,295,000 in research grants, $111,000 in direct research, $575,000 for collaborative and field investigations, $800,000 in professional and technical assistance, $156,000 in review and approval, and $36,000 for overall planning direction and coordination of the programs of this Institute.

Mr. FOGARTY. Thank you, Doctor.

Your appropriation for 1962 is $70,812,000. The request for 1963 is $71,206,000.

Dr. MASLAND. Yes, sir.

Mr. FOGARTY. You are getting only $394,000 over the authorization for 1962?

Dr. MASLAND. Yes, sir.

Mr. FOGARTY. How many people in this country are afflicted with the neurological diseases?

Dr. MASLAND. Approximately 10 million.

Mr. FOGARTY. And blindness?

Dr. MASLAND. That is included in the figure I just gave you.

Mr. FOGARTY. You are getting less than $400,000 more than you had in 1962.

INCREASE IN UNCONTROLLABLE COSTS

This would not even take care of the uncontrollable cost increases, would it?

Dr. MASLAND. This year we have about $3,300,000 of unpaid grants. Is that what you refer to?

Mr. FOGARTY. I meant uncontrollable costs.

Mr. KELLY. There are about $229,000 worth of mandatory costs in this Institute, Mr. Chairman. Your statement would be just about true, if all the funds made available in 1962 were being applied, which is not the case, of course. There is a reserve in this Institute.

Mr. FOGARTY. We have in the past tried to reach a figure of increased costs to carry on research of all kinds. Would you try to get us an estimate on what that will amount to in the Institutes of Health and the entire Public Health Service.

Mr. KELLY. This is a difficult figure and a problematical one.

We have given you estimates before. As a matter of fact, in the statement of training needs that the National Institutes of Health put together for you, a study of total training needs in the medical research area, they do business with this figure showing the extent to which costs of supporting one investigator from the year 1954 to 1960 has increased, and it is just by extrapolating that and projecting it that we can give you anything which even approaches an estimate.

Mr. FOGARTY. Give us the best estimates you can make.

(The information requested follows:)

ESTIMATE OF INCREASED COSTS FOR PUBLIC HEALTH SERVICE RESEARCH ACTIVITIES

Information as to the increased costs in fiscal year 1963 cannot be accurately determined. The following estimate of such costs is, therefore, speculative. The explanation following the table outlines the assumptions used in developing this estimate.

Research grants	$18,054,000
Training grants	3,732,000
Direct operations	2,914,000
Total	24,700,000

The research grants estimate assumes a price increase rate of approximately 4.5 percent and the training grants estimate a rate of approximately 3.1 percent. These estimates are based on the following trend data: (1) Faculty and research professional salaries have risen 7 percent per year, (2) nonprofessional salaries have risen about 4 percent per year, and (3) the index of prices on all Federal purchases of goods and services increased 1.8 percent in 1961. (The rates above were in February 1962 issue of Survey of Current Business, Department of Commerce.)

The estimate for goods and services in the direct operations assumes a further increase in costs of 1.8 percent.

RESERVE OF 1962 APPROPRIATIONS

Mr. **Fogarty.** The reserve for 1962 is $8,512,000, of which $4,942,000 is forced savings.

Dr. **Masland.** That is right.

Mr. **Fogarty.** What accounts for the other $3.5 million?

Dr. **Masland.** This was an Institute reserve.

Dr. **Shannon.** This in part results from some of the programs just beginning this year and the rather late availability of the appropriation, I think primarily in relation to technical assistance. It was calculated that during the initial year it would not be possible to mount a program in the technical assistance area using all the funds available without overobligating the subsequent year's activity.

In other words, in order to end the year with an activity using funds at the same rate as that projected in the budget, it was necessary to develop a program using a lesser amount in the earlier period.

Mr. **Fogarty.** Give us a complete breakdown of the $5 million of forced savings.

(The information requested follows:)

[In thousands]

Activity:	*Directed reserve*
Grants and related contracts:	
Research	$2, 834
Fellowship	57
Training	1, 235
Total grants	4, 126
Direct operations:	
Research	136
Collaborative studies	82
Training activities	25
Professional and technical assistance	500
Review and approval	73
Total direct operations	816
Total directed reserves	4, 942

PROGRAM EFFECT OF RESERVE

Mr. **Fogarty.** You estimate you will have 120 approved research applications you cannot finance because of this reserve?

Dr. **Masland.** That is right.

Mr. **Fogarty.** Do you consider them worthwhile applications?

Dr. **Masland.** We estimate that this number will be recommended for approval by the Council.

Mr. **Fogarty.** You are still short of trained personnel?

Dr. **Masland.** That is right.

Mr. **Fogarty.** This is one area Dr. Bailey spoke of at length. The shortage is still there?

Dr. Masland. Yes, sir.

Mr. Fogarty. Is there a potential for more training if you were allowed to spend the funds which are appropriated?

Dr. Masland. Yes, sir, there is.

Mr. Fogarty. Any question about it in your mind?

Dr. Masland. No, sir.

BUDGET FOR 1963

Mr. Fogarty. The major part of the increase in 1963 over what you are being allowed to spend in 1962 is referred to as an increase for research grants. I see you are asking for only about half enough to finance new applications which will carry forward from the 1962 or be submitted in 1963. Is that right?

Dr. Masland. Yes, sir.

Mr. Fogarty. Do you plan to expand the professional and technical assistance activity from $1.5 to $2.3 million?

Dr. Masland. That is right.

Mr. Fogarty. Is this because of the discussion we just had regarding the reserve?

Dr. Shannon. Within the total allowance it was figured if we were able to expend effectively $1.5 million the carryover would be at the rate of $2.3 million into 1963.

Mr. Fogarty. You have no increase for training or research fellowships?

Dr. Masland. That is right.

Mr. Fogarty. Do you think you can effectively use some additional funds?

Dr. Masland. Yes, sir.

STATUS OF PERINATAL STUDY

Mr. Fogarty. What about your perinatal study? In what year is it now?

Dr. Masland. The original grants were made in 1957. The actual initial completion of cases began in 1959.

Mr. Fogarty. As I understand it the original proposal was for a 5-year program and if necessary it would be 10 years.

Dr. Masland. That is right.

Mr. Fogarty. So we are now in the fifth or sixth year?

Dr. Masland. In the sixth year from the date of the original grant.

Mr. Fogarty. Tell us something of what has happened. I know you have made some discoveries and have come up with some advances.

Dr. Masland. We have now reached the point where approximately 23,000 women have been registered in this study.

Mr. Fogarty. That is only about half what you originally estimated?

Dr. Masland. That is right; about half the number of patients who were considered desirable to achieve meaningful statistical results.

Mr. Fogarty. Why have we not reached that goal of 40,000 to 50,000?

Dr. MASLAND. During the first 2 years of this study we were primarily involved in the recruitment of the participating institutions and in the development of the methodology through which such an investigation could be accomplished. We discovered quite early that we did not have available standardized methods of examination which could give meaningful research information.

For this study to be meaningful each institution has to follow the same method of examination.

Mr. FOGARTY. How many institutions are there?

Dr. MASLAND. Fifteen.

Mr. FOGARTY. I know Rhode Island has participated.

INFLUENCE OF PERSONNEL SHORTAGES

Dr. SHANNON. I would like to comment on a very important factor here.

This development has been retarded unduly because the Institute has been unable to employ personnel in short supply.

Some of the training activities and developmental activities in the 15 hospitals make it necessary for Dr. Masland and his staff to have technicians with investigative research experience to work with each of these groups.

It would be fair to Dr. Masland if the record showed that his inability to employ these people under our salary ceilings has done more to hamper the development of his study—and, in fact, at times has jeopardized its total success—than was anticipated when this study was started some 6 years ago.

I am not at all sure that this study will be satisfactorily completed in 10 years if the current limitation on our ability to employ this type of personnel persists.

Mr. FOGARTY. Do you think there is a good chance of employing this type of personnel in the near future in the numbers needed?

Dr. SHANNON. No, sir.

Mr. FOGARTY. Then the 10-year goal means nothing?

Dr. SHANNON. I would say there is not a chance in the world of completing it in 10 years.

The success of the whole study is in jeopardy right now because of our inability to staff it on a full-time basis and adequately train clinically oriented people.

Mr. FOGARTY. When this study of the Public Health Service, regarding salaries, is complete, and if Congress takes action, do you think that will help?

Dr. MASLAND. If my understanding of what Mr. Folsom's committee will recommend is correct, the answer is "Yes, sir," but——

Mr. FOGARTY. Congress will have to act, too.

Dr. SHANNON. That is correct.

Dr. MASLAND. This is our serious problem. I am very satisfied with the quality of the data we are getting in from the collaborating institutions——

Mr. FOGARTY. We think the one in Rhode Island is working out well.

Dr. MASLAND. They are doing a tremendous job.

Mr. FOGARTY. We have some good contributing groups there.

Dr. MASLAND. That is right, and this is true throughout the collaborating institutions. They have done a tremendous job. It worries me, as Dr. Shannon has indicated, that for us to utilize the data which are being sent in we must have a really top level staff to handle it.

In spite of that we are getting some preliminary indications as to what is going on which is most exciting.

PERINATAL PROJECT DEVELOPMENTS

Mr. FOGARTY. Tell us some things which have developed.

Dr. MASLAND. One of the first things that showed up was the wide variation in the outcome of pregnancy which occurs in different locations, different populations, different institutions. I wish to emphasize that these do not reflect necessarily the medical care of the institution. They are a reflection of many different factors.

For example, the stillbirth rate in one institution is 10 per thousand. In another it is 40 per thousand, four times as many stillborns.

The infant death rate is 18 per thousand in one institution and 40 per thousand in another, twice as great.

The incidence of abnormality, gross abnormality, at the eighth month examination is only a half percent in one institution as against 6 percent in another. This is based on rather small numbers of cases. There are tremendous variations.

Mr. FOGARTY. These figures resemble somewhat the infant mortality rates from hospital to hospital.

Dr. MASLAND. That is right.

There is another interesting thing. Within a given income range there is a difference in the infant mortality rate depending upon the occupation of the mother.

It seems to me that this type of information is an indication that for some reason or another we are not doing the best that we ought to be able to do.

These variations indicate in one place the outcome is not as good as it is in another.

Mr. FOGARTY. You mean by that that those in the lower income groups have more mentally retarded children than those in the higher salaried groups?

Dr. MASLAND. It is not necessarily related to income although this is in fact true.

Mr. FOGARTY. I was always told it made little difference.

CAUSES OF PREMATURITY

Dr. MASLAND. The overall incidence is higher.

We do have a few clues, and again these are the beginning findings, as to the types of factors. I spoke last year about smoking. These findings are still holding true—women who smoke have an 11.6 percent incidence of prematurity. Among women who do not smoke the incidence is 7.7 percent.

We have to emphasize that we cannot say it is the smoking that does it. We can say that the woman who smokes is more likely to have a baby weighing under 5 pounds.

Urinary tract infection seems to be important. In one series of cases the women who had urinary tract infections had a 20-percent prematurity rate as against 4 percent in a comparable group of women who had not had such infections.

We are finding a very high frequency of infection of the umbilical cord and the placenta in instances of prematurity.

Apparently this is related to infections of the vaginal tract during pregnancy. This is important because if this is really true then it puts the finger on a condition which deserves far more concern and far more active treatment than it is at present receiving.

Mr. Fogarty. Are not most of these infections those which can be cleared up if discovered in time?

Dr. Masland. That is the idea.

We are also concentrating heavily on the study of virus infection and its possible relation to pregnancy outcome.

Seven percent of the women in this study have an active virus disease during pregnancy. By active virus disease I speak of the ordinary viruses such as Dr. Andrews has been discussing—colds, flu, and so on.

We are trying to determine which, if any, of these infections do have a relationship to injury of the baby.

Of course, we know that German measles does.

Probably one-third of women who have German measles in the first 2 months of pregnancy will either have a miscarriage or a defective baby as a result.

There is another virus which seems to be bearing some significance. Out of 20 abortions that were studied in this study 2 of them had infection with a so-called salivary virus, which is a mild ordinarily harmless virus which is rather common in the population. In a series of 200 controls, only 1 had this virus, so it may have had some relation to the abortions.

ROLE OF NEONATAL ASPHYXIA

We have information on the role of neonatal asphyxia, that is, suffocation at birth.

We are studying the brains of any children who die in this project. There are now 1,000 such specimens. One hundred have had complete examination. We are getting some very valuable information on normal rates of development of the brain.

For example, the brains of babies whose mothers have diabetes are consistently smaller than the brains of the normal children, in spite of the fact that the babies are bigger and the babies weigh more.

These are just the beginnings of the types of analyses we are carrying forward in this study. There have been over 50 scientific publications this year from the collaborating institutions.

As you know, this study also is being paralleled by the investigation in Puerto Rico.

PROBLEMS OF DATA ANALYSIS

Mr. Fogarty. So you are satisfied that out of this 6-year period you have made some real progress? At least you are getting information which you otherwise could not have gained.

Dr. MASLAND. I would not say I am satisfied. I feel there is much more data here——

Mr. FOGARTY. I mean you are not satisfied progress is being made?

Dr. MASLAND. Yes, sir.

Mr. FOGARTY. Why are you not satisfied?

Dr. MASLAND. We have much more data available for analysis than we have so far been able to interpret.

Mr. FOGARTY. Is the main reason the salary structure?

Mr. MASLAND. I think that is a contributing factor.

Mr. FOGARTY. Within the salary structure under which you are now living is there anything this committee can do to help you get additional personnel to make this evaluation?

Dr. MASLAND. May I prepare a statement on that? I will have to think that one through.

Mr. FOGARTY. Very well.

(The information requested follows:)

PROBLEMS OF RECRUITMENT OF STAFF FOR COLLABORATIVE PROJECT

Recruitment problems for the central staff of the collaborative project stem from four chief causes. First is the low salary level for the type of highly qualified professionals essential to the success of this study. Salaries for such personnel are 20 to 30 percent below comparable positions in nongovernmental institutions.

The second problem has been an unfavorable working situation in rental space in Silver Spring—an isolated situation interfering with effective contact with the scientific community at Bethesda. The construction of the new NIMH-NINDB basic research laboratories, authorized by the Congress last year, will alleviate this problem. The plans for the laboratories already have had a most favorable influence on recruitment; however, completion of this building cannot be accomplished before 1965 or 1966.

A third problem lies in the nature of the job itself, which requires a continued high level effort, but with long-range rather than immediate personal and research rewards. The continued experssions of interest and concern on the part of this committee, with assurances of a determination to support the undertaking to a successful conclusion, have been most helpful. Without such support, recruitment of personnel for long-term appointments would have been impossible rather than simply difficult.

Finally, we are confronted with a serious shortage of trained research personnel, especially in the field of pediatric neurology. The continued support of the clinical and basic research training programs, as outlined elsewhere in this testimony, will insure increasing availability of personnel for the continued development of this important program.

COLLABORATIVE PERINATAL RESEARCH PROJECT

Mr. FOGARTY. We shall place the special report on the subject in the record.

(The report follows:)

SPECIAL REPORT: THE COLLABORATIVE PERINATAL RESEARCH PROJECT

THE PROBLEM

Neurological disorders of infancy and childhood rank high among the Nation's most serious public health problems. These disorders include cerebral palsy, mental retardation, congenital defects of the nervous system, and congenital deafness and blindness. As a group they afflict more than 6 million Americans, many of whom have been seriously disabled throughout their entire lives.

In addition to those already afflicted, some 250,000 babies are born each year with these disorders. Despite our advances in treatment, care, and rehabilitation, many of them will never be able to earn a living and will impose a heavy economic burden on their families, communities, and the Nation for years to come.

THE PROGRAM

To help solve this problem, the National Institute of Neurological Diseases and Blindness is now spending more than $11 million to support a wide range of research projects in a broad scale effort to increase our knowledge of the causes, treatment, and prevention of neurological disorders of infancy and childhood.

The Institute's major endeavor in this area is the collaborative perinatal research project. Launched as a broad approach to a national problem, the project has been in operation 5½ years, including 2½ years of extensive preparation. Its primary goal is to discover clues to the causes of cerebral palsy, mental retardation, and related disorders. To this end, teams of medical and allied scientists at 15 medical centers throughout the country are studying expectant mothers from early pregnancy through labor and delivery, and are examining their babies periodically from birth through school age. As analysis of the information collected reveals suspicious factors, they will be tested and their role evaluated.

A long-term venture in medical research, the collaborative project will eventually involve some 50,000 expectant mothers and their children. This is the minimum number that must be studied if the project is to produce valid results that can serve as a basis for further research aimed at an effective program of prevention.

In 1961 data were collected on slightly more than 9,000 pregnancies, and about 8,600 babies were born to mothers enrolled in the project. This increased the total number of participants in the study to about 23,000 mothers and 17,000 children. At the present rate of enrollment of new patients, it is expected that the goal of 50,000 cases will be reached early in 1965.

EARLY FINDINGS

Useful findings are beginning to emerge from the collaborative project. These findings, however, are preliminary and should therefore be viewed with caution.

Prematurity is one of the most important factors in brain damage and deaths among infants. Prematurity is usually defined in terms of birthweight. In a recent review of data collected on about 7,500 project mothers, the relationship between their cigarette smoking history and the birthweight of their infants was investigated. It was found that birthweights were generally lower among smokers than among nonsmokers. More specifically, the incidence of prematurity (defined as a birthweight of less than 2,500 grams) was significantly greater among expectant mothers who smoked than among those who did not smoke. In addition, the decrease in birthweight was proportional to the reported amount of smoking. These findings, derived from observations on a broad population base, confirm the results of previous studies which have shown a relationship between smoking and prematurity.

Another analysis carried out last year focused on the association between lack of oxygen at birth and abnormal development at 8 months of age. This analysis revealed that 33 percent of infants with an abnormal or suspect performance on the project 8-month psychological examination had shown evidence of lack of oxygen at or soon after birth. In suspect infants, the incidence of oxygen lack was 22 percent and in definitely abnormal infants the incidence was 44 percent. In a control group of infants whose performance at 8 months was normal, the incidence of lack at birth was only 7 percent.

These differences are significant and implicate oxygen lack at birth as a factor in abnormal development which can be identified at 8 months of age by means of a psychological examination. Similar findings have been reported by other investigators, but on the basis of birth data collected after the children had been diagnosed as abnormal. The project findings, on the other hand, are based on data collected at birth and are therefore more meaningful.

A closely related analysis was made to determine whether there is a relationship between psychological findings at 8 months of age and neurological findings at 1 year. Such predictive data have long been needed in the field of infant and child neurology. This analysis disclosed that there is a relationship between overall diagnosis at 8 months and some forms of neurological abnormality at 1 year. There is substantial agreement between the psychologist and the neurologist particularly when both look at areas of development rather than at symptoms, even when they do so 4 months apart. Additional analyses along these lines are being conducted using data collected at birth and at 4 months, as well as at 8 months and 1 year.

As part of an investigation of stillbirths and infant deaths in the project, a study was made of the postmortem findings on a group of children born to mothers with diabetes. This study confirmed the generally known fact that infants of diabetic mothers weight slightly more than infants of nondiabetic mothers. It was found, however, that the brains of infants of diabetic mothers do not show a corresponding increase in weight or volume but, on the contrary, tend to be smaller than the brains of infants of nondiabetic mothers. This discrepancy, moreover, is even greater when dehydrated brains are compared. These findings have considerable practical as well as theoretical importance. Many more cases will have to be studied, however, before they can be considered statistically valid.

Data on the pattern of development of the human brain, and on the rate of growth of its various parts, are almost nonexistent. To help fill this serious gap, the brains of all stillbirths and of all full-term babies dying in the project are being measured. Much valuable information has already been obtained on the development of the brain from the fifth fetal month on. This preliminary information indicates that measurements have more value in determining normal brain development at a given age if they are made on dehydrated brains.

RELATED STUDIES

In 1961 about 50 scientific articles were published presenting findings derived from related studies being carried out at the cooperating hospitals with collaborative project support. These findings relate to subjects as the rule of maternal infections in abnormal pregnancy outcome, the identification of "high risk" mothers, and the early detection of neurological abnormalities of infancy and childhood. The findings described below represent only a small sample of the total reported.

Prematurity has been linked in some cases to an infection of the urinary tract of pregnant women. The infection produces no symptoms and cannot be detected by routine urine analysis. Detection is possible, however, by means of a special urine test. Researchers at two other cooperating hospitals are carrying out similar investigations, and still another related study has been launched to pinpoint the mechanism by which this infection affects the unborn child.

An increased incidence of prematurity and perinatal infant deaths has also been found to be associated with inflammation of the placenta, fetal membranes, and umbilical cord. The study which produced this finding also revealed that an infection of the vagina, or the cervix, or both was present in 50 percent of the patients with inflammation of the membranes and cord, compared with only 20 percent of a control group. This finding points to the possibility that better treatment of infections of the vagina and cervix during pregnancy may reduce the incidence of prematurity and infant deaths.

Investigation of the effect of an Asian flu epidemic on pregnancy outcome has shown that 39 percent of all flu infections occurring in the mothers studied produced no symptoms and were first detected by serological investigation. In addition, 75 percent of the mothers who said they had not had the flu showed serological evidence of infection. The results of this study suggest, moreover, that Asian flu has an adverse effect on the outcome of pregnancy, especially if the infection occurs in the first trimester. These findings point up the need for better methods of detection such as those which have been developed for research purposes in the collaborative project.

A close relationship has been observed between alterations in the concentration of certain proteins in the blood of mothers-to-be and succeeding intrauterine fetal deaths in the second trimester. This finding represents an important advance in the search for methods for the early identification of expectant mothers who may have a high risk of losing their babies.

Studies of young animals indicate that brain damage due to prolonged lack of oxygen is followed by an increase in the permeability of the blood-brain barrier to certain enzymes. The resulting rise in the concentration of these enzymes in the cerebrospinal fluid can be measured and could provide a basis for the early diagnosis of brain damage in children. This aspect is now being explored.

Abnormal eye movements or total absence of eye movements in newborn infants subjected to mechanical rotation has been found to be a sign of abnormality of the nervous system. The test developed for this study should become a valuable part of the clinical neurological examination of newborn infants.

Using improved methods, research workers have found that electroencephalograms (EEG's) of newborn infants aid in earlier detection of brain damage.

In addition, visual stimulation used in conjunction with EEG's has confirmed a previous finding that premature babies respond more slowly than normal, and postmature babies respond more quickly than normal. This highly significant difference in response time provides an additional scale for measuring brain maturation at birth.

PROGRAM DEVELOPMENTS

In addition to research accomplishments, the collaborative project had two important program developments in 1961. One concerns the blood-testing phase of the project, the other, the development of an examination for testing speech, language, and hearing functions in 3-year-old children.

The blood-testing phase of the project makes use of antigens—substances which stimulate a chemical defense mechanism in the blood—to test the mother's blood serum for evidence of exposure to certain viruses during pregnancy. If a mother has been infected, this fact will be indicated by a greater number of antibodies in her blood.

At each of the collaborating medical centers, blood samples are taken from the expectant mothers during pregnancy and are sent to the National Institutes of Health laboratories in Bethesda, Md., for testing. The blood serum is stored at minus 10° Fahrenheit in two huge, walk-in freezers at the Institute's serum center. Specific information on the mother's pregnancy is kept together with data on the sample of her blood serum. This information will be readily available for checking and rechecking for many years.

To test the blood serum, an extensive panel of more than 100 viral antigens have been produced. These include 28 ECHO viruses, 30 Coxsackie viruses, 28 adenoviruses, 9 myxoviruses, and 3 polio viruses. These range in severity from common cold viruses to those that cause paralysis and death. As new virus infections are identified in the cities where the project is being carried out, new antigens must be produced.

Development of the antigens has required extensive work in bringing together specific viral materials, performing many complicated tests, developing new tests, and in many instances developing suitable conditions to grow the virus for antigen production. In addition, a microserological technique has been devised which reduces the volume of viral antigen required for testing to about one-eighth of that required with previous techniques. Since the viral antigens being used in this investigation are rather costly, the new microtechnique will save money.

Large-scale testing has been started using blood serum samples from mothers of abnormal children and from a matched control group. Testing to date has suggested several possible associations between virus infections during pregnancy and certain abnormalities. The data are very limited, however, and no specific associations or presumptive hypotheses can be made at present.

For many years various kinds of examinations have been used to assess speech, language, and hearing functions in children. When these examinations were found to be unsuitable for use in the collaborative project, a group of specialists from the cooperating hospitals was given the task of developing an adequate examination. Their efforts have resulted in an examination for testing speech, language, and hearing functions in 3-year-old children participating in the project.

The examination, which is now being pretested at several of the collaborating medical centers, has three purposes. It will be used primarily as a screening test to spot subtle neurological defects which might have been missed at earlier examinations. It will also provide data for use in confirming or rejecting the results of previous examinations. And it will furnish valuable information for use in describing disorders of the central nervous system as they are manifested in the speech, language, and hearing area. In this connection, it should be noted that the prognostic importance of deviations from the normal pattern of speech, language, and hearing development identified in 3 year olds requires a reexamination of these children at age 6 to 7.

FUTURE PROSPECTS

Major efforts in the future will be concentrated on data processing and analysis. In fact, the prospects for these activities are such that many additional findings are expected to become available during 1962.

Present plans call for focusing attention on such problems as prematurity (as defined by birthweight), toxemia as a major obstetrical complication, the effects of hyperbilirubinemia on the development of prematures, and the relation of specific virus infections during pregnancy to abnormal pregnancy outcome.

In addition avenues are being explored to obtain more information on abnormal pregnancy outcomes by retrospective studies designed to supplement the present prospective investigations of the collaborative project.

MENTAL RETARDATION

Mr. FOGARTY. I think this would also be a good place to put the special statement on your work in mental retardation.

(The statement referred to follows:)

SPECIAL REPORT: MENTAL RETARDATION

THE PROBLEM

President Kennedy's recent appointment of a panel on mental retardation focused the public's attention on one of the Nation's most serious health, education, and welfare problems.

Mental retardation today afflicts an estimated 5,400,000 Americans. Due to the increased birth rate, a decrease in infant deaths, and a longer life expectancy resulting from medical advances, the number is growing. By 1970 it is expected to top 6 million, at least half of whom will be children.

Every year 126,000 babies are born who will be mentally retarded, some of them so severely that they will never even be able to care for their own creature needs. Neither the rich nor the poor, the city dweller or the farmer, the president of a giant corporation or the factory worker, or any part of our society is exempt from the tragedy of the birth of a mentally retarded child. Mental retardation is a national problem and it demands a national solution.

The price the American people pay for mental retardation is enormous: More than $1 billion a year for institutional care of retarded children and adults; for construction of institutional, educational, and community facilities; and for special care in the family home. It costs the Nation another estimated $10 billion a year in lost productivity. The cost in terms of human misery is incalculable.

Efforts to solve this problem are complicated by the fact that mental retardation encompasses many biological, psychological, and social or environmental factors. Indeed, the interplay of these factors ultimately affects every person's development. Because these factors provide a wide variety of potential origins of retardation, research into the causes and prevention of the disorder is especially complex.

Yet the picture is not all black. Two developments hold out hope that the problem of mental retardation can eventually be solved or at least greatly reduced. One is the success to date of medical research in pinpointing some of the causes of mental retardation and in discovering ways of preventing or treating them. The other is the current research attack against mental retardation being carried out by the National Institutes of Health, the major medical research arm of the U.S. Public Health Service.

ADVANCES IN RESEARCH

The age-old belief that mental retardation was due only to a hereditary defect is now known to have been based on nothing more than ignorance or superstition. Bit by bit, medical research workers have uncovered evidence which indicates that mental retardation is not a disease, but a symptom of a disease, of an injury, of a defect in body chemistry, of some obscure failure of development, or even of inadequate opportunity to learn. Just as a fever is a symptom of an infection, mental retardation is a symptom of mongolism, birth injury, infection, or even inadequate stimulation in early childhood. It can be so severe that the afflicted person can never leave protective care or so mild that it is detected only under stress or through special tests.

Except to those parents whose children have been saved from mental retardation, the advances in research over the past decade have not been dramatic ones. There have been a few major accomplishments, but none comparable to that made in the research attack on infantile paralysis. Nor has the picture been one of uniform improvement on all fronts. We still need to learn a great deal more, for example, about the relation of mental retardation to events and conditions of pregnancy, labor, and delivery. We can surely find encouragement, on the other hand, in the knowledge that the following causes of mental retardation have not only been identified, but can be prevented or treated.

Phenylketonuria, or PKU, is a congenital disorder of body chemistry. The child born with PKU lacks the enzyme necessary to metabolize phenylalanine, a chemical found in all proteins. As a result, phenylalanine accumulates in the victim's blood and finally damages his brain. Today we not only have a simple blood test for the early detection of PKU, but we have a phenylalanine-free diet which can prevent mental retardation. Widespread and early use of both the test and the special diet could wipe out this form of mental disability.

The child born with the brain-damaging disorder known as galactosemia, on the other hand, cannot metabolize galactose, a sugar found in milk. As with PKU, a quick test of the blood permits early diagnosis and prompt institution of a diet from which galactose has been eliminated.

Cretinism, a congenital deficiency of thyroid hormone, stunts its victims' mental development as well as their physical growth. Research has shown that this disorder often can be prevented by giving the thyroid hormone to children born with a defective thyroid gland—if the condition is diagnosed early enough.

Until recently, kernicterus, a brain-damaging form of infantile jaundice, was responsible for 1 percent of all annual admissions to institutions for the retarded. The gradual conquest of this crippler of children's minds makes an exciting story. The first important step was the discovery that kernicterus is due to Rh blood incompatability between the mother and the unborn child. This was followed by the development of a technique—exchange transfusion—which makes it possible to wash out of the baby's body the harmful antibodies received from the mother, to replace the destroyed red blood cells with new ones, and to give the infant a fresh start through the precarious first days of life.

There are two brain-damaging conditions which sometimes can be corrected surgically, to save the afflicted child from mental retardation. One condition is premature fusion of the skull bones, the other enlargement of the head due to the accumulation of an excess of fluid within the skull (hydrocephalus). In both instances, the key to prevention of mental retardation is early diagnosis and prompt treatment.

Injection of gamma globulin—an extract of human blood rich in antibodies against measles and some other infections—has been found to reduce both the severity of measles and the risk that the infection will damage the patient's brain. And the administration of massive doses of antibiotics has been shown to be an effective treatment for bacterial meningitis, another infection that can cause mental retardation.

Hypoglycemia, a lowering of the blood sugar level in newborn and young infants, can lead to convulsions, mental retardation, or even death. This tragedy can often be prevented by early diagnosis and adequate therapy.

Penicillin given to an expectant mother with syphilis will not only "cure" her but also safeguard her unborn baby, or cure it if it is already infected. Many cases of mental retardation are being prevented each year by the prenatal blood test and penicillin treatment.

Maternal diabetes has been identified as an underlying cause of some cases of mental retardation. Diabetes can be easily diagnosed by a simple urine test, and adequate treatment can reduce the risk of brain damage.

In the case of German measles early in pregnancy, which has been implicated as a cause of mental retardation, evidence suggests that proper use of gamma globulin may prevent damage to the unborn child. The final solution in this instance, however, depends on the development of specific immunization against this disease.

As encouraging as these advances are, it is evident to all concerned with the problem that much remains to be done before mental retardation can join the long list of human ills that medical science has brought under control.

CURRENT RESEARCH

The present mental retardation research program of the U.S. Public Health Service is centered in two of the National Institutes of Health: the National Institute of Neurological Diseases and Blindness and the National Institute of Mental Health.

Neurological research activities

The Neurology Institute conducts research in mental retardation and related neurological and sensory disorders of infancy and childhood at its Bethesda, Md., laboratories, and supports such research at medical centers across the country through its research grants program. At present the Institute is spending more than $11 million—about one-quarter of its fiscal year 1962 research appropriation—to support 151 projects aimed at increasing our knowledge of the causes, prevention, and treatment of mental retardation and kindred disorders.

In the forefront of the Institute's research attack in this area is the long-term collaborative project on cerebral palsy, mental retardation, and other neurological and sensory disorders of infancy and childhood. The project has been in operation 5½ years, including 2½ years of careful planning and extensive preparation. Its primary goal is to identify those biological and medical factors operating between conception and birth which may be associated with mental retardation, cerebral palsy, congenital defects of the nervous system, and congenital blindness and deafness.

To this end, 15 hospital teams of medical and allied scientists are studying expectant mothers from early pregnancy through labor and delivery, and are examining their children periodically from birth through school age. By the end of 1961, data had been collected on about 23,000 mothers and 17,000 children. The project will eventually involve some 50,000 mothers and their children in many parts of the country. This is the minimum number that must be studied if the project is to produce statistically valid results. As analysis of the information collected reveals suspicious factors, they will be tested and their role evaluated.

The project has already produced useful preliminary data showing that the incidence of neurological disorders among infants and children taking part in the study may be higher than was expected. In addition, a recent analysis of data collected on 7,500 pregnancies has shown an association between cigarette smoking and prematurity, which is an important factor in brain damage and deaths in infancy. Prematurity is usually defined in terms of birth weight. In this series of cases, the decrease in birth weight was proportional to the number of cigarettes smoked daily. This result confirms previous reports on the relation of smoking to birth weight.

In addition to the long-term collaborative project, institute scientists at Bethesda and institute grantees at medical centers throughout the country are conducting a wide range of research projects aimed at saving children from mental retardation. These include studies of chromosomes in Mongoloids and in patients with congenital malformations, biochemical and microscopic investigations of the brain and nervous system, methodological studies on techniques for the early detection of neurological defects, projects on causative factors such as oxygen deprivation and jaundice in newborn infants, and investigations of toxic and metabolic deficiency disorders and developmental defects.

Other studies are being carried out at the institute's primate center in Puerto Rico, where deliberate laboratory efforts have been made to produce mental retardation in animals. Important investigations have been conducted at the Laboratory of Perinatal Physiology, and others are planned to demonstrate the effects of harmful agents on the developing animal and to observe the characteristics of the mental retardation which they may produce.

Mental health research activities

The National Institute of Mental Health also conducts and supports a wide range of studies aimed at increasing our knowledge of the causes, prevention, and treatment of mental retardation.

Much of the basic research conducted at the Institute's Bethesda laboratories is directly related to mental retardation. Great stress has been placed on investigations of the brain-damaging disorders of body chemistry, such as phenylketonuria. Biochemists, for example, are examining both the metabolism of the child with PKU in relation to his total growth and development and the action of the chemical, phenylalanine, which in excessive amounts can cause brain damage.

The Institute's Biosocial Growth Center is conducting a series of studies of parents and children aimed at shedding light on the psychological factors in mental retardation as well as in normal growth and development. A closely related investigation is focusing on differences in family relationships among the various socioeconomic groups.

Through its research grants program, the Mental Health Institute is supporting in the present fiscal year a total of 88 studies at a cost of $2.8 million. In the biological sciences these include studies on the metabolism of fats, proteins, carbohydrates, and other substances which are known to play, or are suspected of playing, a role in such brain-damaging disorders as phenylketonuria, galactosemia, and maple sirup urine disease. Attempts are being made to produce these inborn errors of metabolism in animals, in the hope that what is learned from animal studies will benefit human beings. Spurred on by the recent discovery of a chromosomal abnormality in Mongolism, other investigators are peering into the chromosomes to increase our knowledge of their effects on human behavior.

In the psychological and social areas, the Institute is supporting a number of studies on the development of language and speech in retarded persons, including an examination of differences in speech patterns between the institutionalized and the noninstitutionalized child. Studies on learning in the mentally retarded include investigations of the effectiveness of various teaching methods, such as the use of machines in teaching retarded children reading, arithmetic, and other basic subjects. Other grant-supported research has to do with the effect of a mentally retarded child on his brothers, sisters, and parents.

FUTURE PROSPECTS

It is only in the past half-dozen years that the American people have begun to rise to the challenge posed by mental retardation. Most of the credit for this development belongs to those scientists, Members of Congress, Government officials, and private citizens who, refusing to accept mental retardation as an unalterable fact of life, have worked for the creation of programs of research and service for the mentally retarded. As a result we have come a long way in our methods of caring for the retarded: from the dark attic to the isolated State hospital to the community-based residential care center and the day-care school. We have come a long way, too, in our attitude toward mental retardation: from an attitude of despair based on ignorance to an attitude of hope based on research. We have discovered the causes of some forms of mental retardation as well as ways of preventing or treating them. We have every reason to believe that we will discover more.

Further advances in the attack against mental retardation will depend on our meeting two great needs. The first great need is for increased application of present knowledge of the causes and prevention of mental retardation and related forms of reproductive failure. Many medical scientists are convinced that better preparation of young people for marriage and parenthood, good prenatal care for more expectant mothers, and good postnatal care for more infants and children would strikingly reduce the toll now taken by disorders of infancy and childhood, including mental retardation. Responsibility for the development of programs desgined to cut down the present costly time lag between the discovery and use of medical knowledge in this area must be borne not only by Federal, State, and local governments but by medical schools, professional medical associations, and the individual physician. The individual citizen, moreover, has a responsibility to take advantage of available services.

The second great need is for a national program in the field of mental retardation—national in the sense that it would enlist and coordinate the efforts of all levels of government, voluntary and professional organizations, a multitude of scientific disciplines, and many individuals. It was such an approach that the President had in mind when he called the Panel on Mental Retardation.

The primary objective of a national program would be the prevention of all possible cases of mental retardation. Failing total prevention, its objective would be early diagnosis and treatment, followed by coordinated programs of education, rehabilitation, and psychological adjustment.

To achieve these ends will require an increase in professional and supporting personnel for research and service. Basic, applied, and operations research in all areas must be broadened and accelerated. New service programs, demonstration-evaluation projects, and other activities will have to be provided for the individual, the family, and the community.

New methods of coordination can start on the Federal level. But systematic cooperation among Federal, regional, State, and local agencies must be developed in order to set priorities and standards. To some extent, this is being done. It needs to be accelerated and coordinated. There are major resources now at our disposal in the Department of Health, Education, and Welfare. They need to be coordinated and focused on such specific problem areas as personnel, research, standards, and services. In this endeavor, the President's Panel on Mental Retardation, composed of outstanding physicians, scientists, educators, lawyers, psychologists, social scientists, and civic leaders, will undoubtedly contribute useful guidelines and recommendations for action.

With the advice and consultation of many public and private agencies, the details of each aspect of a national program can be developed. We can move forward only if we set our goals high and use our abilities and ingenuity to plan and to allocate our total resources, to the end that every child may someday be assured as full and useful a life as possible.

CONTRIBUTIONS OF PERINATAL RESEARCH PROJECT

Mr. FOGARTY. Was not this study considered one of the real basic starts in research as to the causes of mental retardation and cerebral palsy?

Dr. MASLAND. Yes. Aside from the data, the influence in these teaching institutions is very great.

Mr. FOGARTY. Are you having any problem getting the women to cooperate with you?

Dr. MASLAND. None whatsoever.

Dr. SHANNON. This problem has broad significance. I am reminded that when we were testifying before the Interstate and Foreign Commerce Committee last week, a fact which repeatedly came up for discussion was that the United States is something like sixth or eighth in the list of advanced countries with respect to their excellence in handling infants and young mothers as measured by infant mortality rates.

Studies such as these have already given us clues as to what areas should be emphasized in education and what health practices should be emphasized in order to stop a trend which is very undesirable. One can reduce infant mortality when it is very high by a series of very obvious things, but when one gets to the point where practices are good but not good enough any further improvement requires highly specific information as to what should be emphasized.

These studies may show us what we should work on. I think this secondary information will be equally as important as the primary purpose of the studies.

STATUS OF PUERTO RICO PROJECT

Mr. FOGARTY. Doctor, tell us about your project in Puerto Rico. Are you satisfied with the progress they are making?

Dr. MASLAND. The activity in Puerto Rico, as you will recall, was established to parallel the program being conducted in this collaborative project we just discussed.

The limitation of this research is the fact that obviously you cannot experiment with human subjects.

There was a need, then, to be able to study in animals the types of factors which we suspect are operating in humans.

I mentioned earlier that suffocation of the baby seems to be an important factor. We cannot experiment with suffocation of human babies. We have to have some animal in which we can conduct actual experiments in respect to the management and treatment of this type of a complication.

The monkey is uniquely suited for this because of the fact that the reproductive process of the monkey resembles very closely the reproductive process in humans. This is not true of other animals.

During the 5 years we have been operating the activity in Puerto Rico we have reproduced cerebral palsy and mental retardation in monkeys. We have demonstrated that this can be produced simply by suffocation.

We are now working on methods to modify the results. There are some encouraging indications that by giving sodium carbonate and glucose to the baby at the time of this suffocation the degree of damage can be reduced.

We have obtained a much clearer picture of the nature of the process and the parts of the brain which are involved. I think we have demonstrated quite clearly that certain unusual disabilities of hearing and perception are very commonly the result of asphyxiation and neonatal jaundice.

We are starting some studies regarding the effects of jaundice in these new born monkeys, and we are able to duplicate cerebral palsy due to kernicterus from jaundice.

One of the very important investigations which is now underway is the study of virus infections in pregnancy.

You spoke earlier of virus-free animals. We do not have virus-free animals. Dr. Shannon has pointed out that you cannot do this until you know all the viruses and can test for all of them.

The monkeys we have in Cayo Santiago in the free-ranging colony, all of whom have been born on that island, and who have had very limited contact with other animals or with humans, we find are remarkably free of viruses.

We recently had them tested against a whole range of almost 90 different human viruses. To the best of our knowledge they had been exposed to only three of these viruses. They had no antibodies against measles. They have no antibodies against some of the tumor viruses.

These animals are proving extremely valuable as animals against which you can test a suspected infectious agent.

For example, if you have a person with German measles and you take a sample of saliva, you assume this saliva has a virus in it. We have no place to test this because we have no humans, or very few humans, that we know never have had German measles, and we have had no animals that we know have not had German measles or that we know are susceptible.

However, the monkeys in Cayo Santiago presumably never have been exposed to this virus and are, therefore, very suitable subjects on which to test new infectious agents.

We have a very important program of this sort now in operation.

ESTABLISHMENT OF ADDITIONAL FACILITIES

Mr. **Fogarty.** If this is so important why have we been so slow in getting monkey colonies started on these other two islands?

Dr. **Masland.** We have now acquired two additional islands. I visited there last week. Those islands are ready to receive the animals.

Dr. Koford is now in India and we expect to have 300 monkeys within the next 6 months.

We took 8 monkeys from Cayo Santiago and turned them loose on one of the islands to see how they would adapt before actually shipping other monkeys in. They seem to be doing quite well.

MULTIPLE SCLEROSIS

Mr. **Fogarty.** You told us you had some good news about multiple sclerosis.

Dr. **Masland.** Not so much good news as some very important observations.

Mr. **Fogarty.** I was just hoping.

Dr. **Masland.** I don't want anyone to feel we have a treatment for this disease. We do not.

Mr. **Fogarty.** You have not made much progress in the last 10 years, however. If you have made some this year, I would be pleased to hear it.

Dr. **Masland.** The really important clue in multiple sclerosis is its geographical distribution. It is a real detective problem.

It is quite clear that multiple sclerosis is a disease of cold climates. It does not occur in the tropics. This has now been established.

Among individuals who have moved from the tropics to a cold climate, the first case of multiple sclerosis has been found to appear as early as 3 years after they move.

On the other hand, people who have lived in a cold climate, who move to the tropics, may develop multiple sclerosis in the tropics even as long as 9 or 10 years after they move there.

The really key question is this: What is there that exists in a cold climate which, operating over a period of 3 years, will cause a person to have multiple sclerosis and which does something to a person which continues to operate for periods up to 8 years after they get to a warm climate?

There are many possible explanations for this. I think really the most likely is that this is an infectious process—a virus or other agent which is present in the more temperate climates, which has a very long latent period, and which causes these late effects.

This distribution parallels rheumatic fever, for example, it parallels the distribution of many respiratory viruses.

One of the things that makes this seem more probable is the discovery in animals of some very slowly developing virus diseases. I think last year I spoke of scrapie, a disease of sheep. If the sheep is inoculated with scrapie, it may be 2 years before it develops the disease. The virus lurks in his nervous system for this period of time.

I have just come across another very interesting observation. About 2 years ago the director of a very large zoo said to me, "There is a very peculiar disease of our monkeys. They are developing a neurological disease."

As you know, we have never seen in animals anything like multiple sclerosis. This picture of a sudden episode of blindness, paralysis, tremor, then improvement, then another episode with some other part of the nervous system affected and then improvement. We have not seen this in animals.

He has brought to our laboratory now several monkeys who have a very interesting picture. They have an illness with a series of convulsions, development of paralysis and blindness. Then this seems to improve for a while and they have another episode, get worse, and eventually they die.

This has some features which are not identical with multiple sclerosis. Convulsions are not a common feature, but it has very important resemblances to this disease.

I think one of our most important moves is that of establishing and developing a program, which we have already started, for an active effort to culture viruses from patients with multiple sclerosis.

Mr. Fogarty. You consider this a real good lead?

Dr. Masland. I do.

POSSIBILITY OF STEPPING UP PROGRAM

Mr. Fogarty. How can we help you to redouble your efforts in this area?

Supply for the record what you can do if you had more funds and how much you think you can use.

(The information requested follows:)

Additional Requirements for Studying Certain Chronic Diseases of the Nervous System

An opportunity exists at this time for an all-out organized effort to detect any viral or infectious agents possibly responsible for certain chronic diseases of the nervous system. Such diseases include multiple sclerosis, chronic epidemic encephalitis (Parkinsonism), some encephalitides of childhood, and certain infantile convulsive disorders.

The isolation of such agents is likely to be difficult. The diseases obviously have a prolonged incubation period—the inoculated animal must be observed for periods of years to await the appearance of disease. Susceptible strains of animals must be used, and it may be that these diseases will occur only in primates.

As an initial step, it is proposed to establish four centers to search for the cause of multiple sclerosis and the encephalitides. These centers would be equipped with facilities for the long-term observation of inoculated animals, and with laboratories for small animal and tissue culture work. It is hoped that one such unit might be established in Puerto Rico in conjunction with the Perinatal Laboratory, and that a specialized island colony might be reserved as a source of disease-free animals. An additional unit should be located overseas in order to make possible a diversity of geographical environments, and to utilize the availability of patient material from different communities.

The establishment of four such units would require $1,200,000 in 1963. The facilities at Puerto Rico could be developed within the proposed budget. However, some additional laboratory space above that now projected would be required.

Mr. Fogarty. We have discussed this problem for 10 or 12 years. The first year we didn't even know how many people in this country had multiple sclerosis. If you have a good lead I think we should explore it to its fullest extent.

We will insert your special report in the record.

(The report referred to follows:)

Special Report: Multiple Sclerosis

THE PROBLEM

An estimated quarter of a million Americans are affected by multiple sclerosis, a chronic and progressive disease of the central nervous system. Another quarter of a million are believed to suffer from related disorders.

In multiple sclerosis, the white fatty substance called myelin, which forms an insulating sheath around the nerve fibers, is dissolved or destroyed in scattered areas of the brain and spinal cord. Lost myelin fails to regenerate and is replaced by scar (sclerotic) tissue which impedes or distorts transmission in the affected nerves to the parts of the body which they control. Repeated attacks causing lesions in the brain and spinal cord usually produce more severe nerve dysfunction.

Despite more than a century of study, the cause of multiple sclerosis remains unknown. No generally effective treatment has been found to halt the destructive process known as demyelination.

Although the onset of the disease may be gradual and progressive, more often sudden neurological symptoms, such as disturbances of vision, incoordination, numbness or paralysis, become apparent when the disorder is present.

So far, scientists remain baffled by three intriguing facts about multiple sclerosis: It affects mainly young adults, it occurs most often in episodes, and it is more common in cold climates than warmer areas. Although the onset may occur at any age, the disorder appears most commonly between the prime ages of 20 and 40 years.

Paradoxically, the disease occurs most frequently in episodes. A period of worsening is generally following by a period of improvement, but each later attack usually causes slightly more disablement than before. The course of the disease is highly unpredictable. Some persons with this condition, following one or more episodes, appear to have a remission and experience no further difficulty during the rest of a normal lifespan.

Another puzzling aspect of multiple sclerosis is its strikingly higher prevalence in colder regions than in warmer zones. Multiple sclerosis is common in Canada, less common in northern United States, and very rare in the southern and warm climates. In other countries, the prevalence of multiple sclerosis also varies mysteriously with geographic latitude. No evidence exists that moving to a warmer climate from a colder area will control or cure multiple sclerosis once it has occurred.

Suspected but still unproved are different possible causes of multiple sclerosis. Among many theories proposed are: alterations in the way the body uses food; exposure to extremes of heat or cold; inadequate blood circulation; a genetic factor; toxins; nutritional deficiencies; viruses; and a hypersensitivity. Many scientists believe that several factors, operating as links in a causative chain, may be implicated in multiple sclerosis.

RESEARCH ACCOMPLISHMENTS

A number of important advances have been made in multiple sclerosis research by Institute scientists and grantees and by other investigators. Studies of the chemical and physical processes related to myelin formation and liquefaction have produced significant gains in basic knowledge. In summary:

Institute scientists discovered how an essential lipid compound in the myelin sheath is formed in the body and how to synthesize this compound, sphingosine, in the test tube. This achievement contributes to studies of the disintegration of the myelin sheath and may prove a step toward discovering how this phenomenon—demyelination—may be reversed.

Techniques were developed for reproducing in experimental animals an inflammatory disease of the nervous system, allergic encephalomyelitis (EAE), which resembles certain human demyelinating disorders. This disorder in animals occurs when the body develops an autoimmunity and becomes sensitized against certain substances normally occurring in the brain; namely, the myelin sheath which surrounds the nerve fiber. The liquefaction of this myelin sheath which occurs in the experimental disease bears some resemblance to that which occurs in multiple sclerosis. Study of this experimental disease is therefore of great importance.

Other areas of research attention in recent years include the search for some toxic or infectious agent, or a virus, which may trigger the destructive process. The discovery of infectious diseases in sheep and goats which resemble multiple sclerosis, and are characterized by latent periods up to several years after infection, has stimulated interest in the possibility of a viral agent, which may infect many but affect few.

CURRENT RESEARCH ACTIVITY

Significant research gains of importance to multiple sclerosis have developed recently. Investigators have isolated from brain tissue the chemical agent responsible for the experimentally induced disease, allergic encephalomyelitis. Institute and other researchers have now identified the causative agent as a small basic protein which is found in the myelin sheath in the brain. They have discovered that the same protein that produces the experimental disease, when injected into the skin with a special emulsion which enhances the action of the protein, can specifically delay or prevent symptoms of the disease when given without the adjuvant.

Modification of the protein changed its characteristics so that it no longer induces the disease but still protects the animals. The mechanism underlying this inhibition has not yet been clearly defined. However, the new finding supports the theory that demyelination may be induced by autosensitization, and it provides important clues toward understanding the initiating event that occurs in spontaneously demyelinating diseases. Moreover, the discovery that allergic encephalomyelitis can be suppressed by immunologic techniques strengthens hope of a possible approach to controlling multiple sclerosis.

Another provocative research advance is that this experimental disease (EAE) can now be studied in tissue culture. If serum from an animal suffering from the experimental disease is applied to a tissue culture containing nervous tissue, liquefaction of the myelin sheath can be observed. Presumably the process in tissue culture is similar to that which takes place in the brain of an animal afflicted with the disease.

This year it has been reported that serum from certain patients suffering from multiple sclerosis is also capable of causing liquefaction of myelin in tissue culture. These preliminary findings require further confirmation but provide increased evidence of similarities between multiple sclerosis and allergic diseases of animals.

Of significance this past year is the first demonstration of remyelination in adult mammalian central nervous tissue, reported by an Institute grantee working with other investigators on a study involving experimental lesions in the spinal cord of adult cats. Earlier, investigators found that regeneration of myelin is possible in the peripheral nervous system. In this study, investigators suggest that myelin can be reformed around demyelinated nerve fibers. From this and other studies may come important new knowledge on the mechanisms of myelin formation in humans.

The peculiar geographic distribution of multiple sclerosis is believed to hold some important clue to its cause. With the climatic factor in mind, an international group of scientists including Institute grantees, continues its task of formulating a global epidemiological study on this demyelinating disorder.

Over many years, repeated efforts to find an infectious agent in patients with multiple sclerosis have failed. However, interest in the search for viruses in multiple sclerosis has recently been revived through the discovery that viruses may remain inactive in the nervous system for long periods of time. Two animal diseases, previously thought by some investigators to be genetic in origin, have now been demonstrated to be due to such latent viruses. These diseases—"scrapie" and "visna"—have a long initial latency and a slow, progressive course.

Demonstration of a viral agent is a long and difficult process. Discovery of the known viral cause of a number of diseases has come only after many failures. This could be the case in multiple sclerosis. Proof could be accomplished only with difficulty, because as in the case of "scrapie" and "visna," the virus may have a long incubation period. It may be that relatively few infected animals would develop the disease. Therefore, observations of inoculated animals over a prolonged period of time and in an environment free of intercurrent infection would be necessary to determine whether multiple sclerosis is or is not due to a virus.

PROSPECTS FOR THE FUTURE

Researchers are trying not only to unravel the basic causes of multiple sclerosis, but many are busily seeking to discover a cure. If it can be learned what causes spontaneous remissions to occur, then science should be able to find a way to create permanent remissions. Although the process of remission is still unknown, some clues to the responsible mechanism have already been found. Hopefully, scientists look forward to the development of an effective cure for multiple sclerosis.

Meanwhile, better guidelines in testing drugs for treating multiple sclerosis may be expected. The panel of scientists named to evaluate drug therapy has published its preliminary report. It is now attempting to develop a classification of different phases of the disorder and to plan other aspects of a special program to test currently available treatments. Clinical investigators are convinced that a carefully controlled study—one that systematically compares the effects of different treatments over meaningful periods of time—is the only reliable basis for evaluating treatment.

Increasing resources of this Institute and at grant-supported research centers are being applied in the program to conquer multiple sclerosis. Investigators are seeking, among other goals, to understand the chemistry and anatomy of myelin, to pursue studies of autoimmune reactions which may lead to methods of prevention, to identify a viral agent that might be responsible for the disease, to understand the significance of its strange geographic pattern, and to study its incidence in other populations of the world.

The scope of this Institute's effort, translated in dollars and individual projects since fiscal year 1959, is indicated as follows:

Research in sclerosing disorders supported by NINDB

Fiscal year	Extramural		Intramural		Total	
	Number of projects	Amount	Number of projects	Amount	Number of projects	Amount
1959	55	$931, 263	14	$158, 003	69	$1, 089, 266
1960	60	1, 255, 065	14	378, 076	74	1, 633, 141
1961	70	1, 574, 543	12	172, 900	82	1, 747, 443
1962 (estimated)	96	2, 120, 000	14	237, 000	110	2, 357, 000
1963 (estimated)[1]	95	2, 490, 000	16	264, 000	111	2, 754, 000

[1] President's budget.

PARKINSON'S DISEASE

Mr. FOGARTY. What progress are you making with Parkinson's disease?

A few years ago someone told us they were able to induce Parkinson's disease in a chimpanzee. Did anything come from that experiment?

Dr. MASLAND. There are perhaps two forms of Parkinsonism. There is a form which results from a virus disease. That is the so-called chronic epidemic encephalitis which was prevalent after that epidemic in 1918 and 1920.

Mr. FOGARTY. How does that affect a person?

Dr. MASLAND. They develop tremor, rigidity, difficulty with speech, and progressive paralysis. The picture is very comparable.

The other form of Parkinsonism perhaps is not due to a virus. We think this is more likely a chemical defect in certain cells of the brain.

Mr. FOGARTY. How does that affect one?

Dr. MASLAND. Very much the same. This is more likely to affect the older people. It starts with flattening of the facial expression, a stiffness in the gait, and they have a tremor of the extremities and eventually difficulty in speech, stooped posture, and incapacity. This is a very common condition.

Mr. FOGARTY. There are quite a few people in the country suffering from that?

Dr. MASLAND. About 1½ million.

RELATIONSHIP OF TRANQUILIZERS TO PARKINSON'S DISEASE

One of the clues to this is the discovery that some of the tranquilizing agents used for mental illness, in large doses, will produce Parkinsonism.

We are studying the chemical basis of this specific effect.

Mr. Fogarty. What drugs?

Dr. Masland. Tranquilizers—reserpin.

Mr. Fogarty. Has this shown up in some of the State institutions?

Dr. Masland. It has. The importance of the excessive use of the tranquilizers in Parkinsonism is that this provides us with a clue as to the chemical derangement of the brain, which may be responsible for this disease. We know that the tranquilizing agents have their action by modifying the concentration of certain chemicals in the brain. We are assuming, then, that in Parkinsonism there may exist a spontaneous derangement of these chemicals. We are attempting to modify this by giving drugs which react with the tranquilizing group.

Mr. Fogarty. Is there any way to reverse this action once it has happened?

Dr. Masland. Yes; fortunately, the effect of the tranquilizers is ordinarily reversible. There have been reported one or two instances of individuals who received massive doses of tranquilizers in whom the Parkinsonism appeared to be permanent, although this is still under debate.

In general, the effect is reversible when the drug is discontinued or reduced. In addition, we do have a great variety of drugs which are able to reverse the effect. These are the drugs which are used to relieve the symptoms of the spontaneous Parkinsonism.

Mr. Fogarty. Are you working on this chemical reaction of the brain?

Dr. Masland. Yes; that is the approach. Really, one of the most important areas for development of the Institute's total program is neurochemistry, the study of the chemistry of the brain and its modifications.

Mr. Fogarty. Do you think because of this lead you could expand the program in this area to advantage?

Dr. Masland. Particularly in the area of training such people. The field of neurochemistry is a very difficult field. It is essential for us to have more people trained for this highly specialized type of work.

Mr. Fogarty. We shall place your special report in the record at this point.

(The special report follows:)

Special Report: Parkinsonism

THE PROBLEM

The broad view of the problem which Parkinsonism presents to our country has not changed significantly this past year. Estimates of numbers of cases vary from 300,000 to 500,000 and epidemiologists suggest that 25,000 to 43,000 new cases occur each year. The magnitude of the problem becomes greater as the longevity of our population is increased since a large segment of Parkinson's disorders occurs in age groups over 50 years.

Parkinson's disease, although earlier identified by other names, is one of the oldest disorders known to medical science. It was described as early as 2

A.D. There are several forms of Parkinsonism. A form spoken of as "chronic epidemic encephalitis" was observed in epidemic form in 1919–20 in the wake of the great influenza epidemic. It is still not known whether this entity was due to an unusual reaction to the influenza virus, or was due to an unrelated concomitant epidemic that struck shortly after the influenza had passed. Another form of Parkinsonism is seen in industrial miners poisoned with manganese. The cause of most common forms, occurring in later life, is still uncertain.

Parkinsonism has two dramatic symptoms: a progressive and highly disabling muscular rigidity and a distressing uncontrollable trembling. These involuntary movements occur when the individual is at rest or attempts a motion, but disappear during sleep. Other features include a propulsive gait or tendency toward running to prevent falling forward, as well as the reverse, a retropulsion or falling backward. These major problems manifest themselves in many other ways such as inability to turn over in bed or assume new positions, digestive and elimination disturbances, neuralgic pains and aches, headaches, disturbances of vision, drooling of saliva, loss of strength and vitality, development of masklike facial appearance, loss of weight, and speech disturbances. These symptoms are progressive and in most instances gradually produce incapacitation and often complete helplessness.

As is true of so many other chronic neurological disorders, the toll which such crippling disorders takes in terms of burdens and distress to both patient and family, beyond the heavy financial strain, is immeasurable. One writer pointed out that the very nature of Parkinsonism, including its usually unknown etiology, its progressive and chronic nature, and the highly visible symptoms guarantee numerous emotional and mental problems concurrent with the illness.

Since no cure for Parkinson's disease is available, all treatment must be directed toward the control of the symptoms and the proper management of the patient.

RESEARCH ADVANCES

It was not until the latter part of the 19th century that medical investigators found that extracts of the belladonna plant could relax the stiffened muscles and quiet trembling. Following the influenza epidemic of 1917 and an increase of Parkinsonism attention was given to the discovery of drugs which would hold these symptoms in check. Belladonna, hyoscyamine, and stramonium—plant extracts with similar but slightly varying properties—were each found to give some relief. Since World War II, a wide assortment of synthetic drugs has been developed which have brightened the future of some Parkinson's patients. These drugs are more specific in action and less disturbing to the patient than the plant ingredients of hyoscine and atropine upon which all remedies rested a decade ago. A new drug, diphenhydramine hydrochloride, tested this year, seems especially promising. Nevertheless, investigators this year pointed out that, in general, pharmacological treatment of Parkinsonism is severely limited in effectiveness, since at best only 20 to 30 percent reduction of symptoms can be achieved.

Because of the variety of drugs now available, it has become essential that a systematic and scientific program for the evaluation of their effectiveness be developed. In the proceedings of an Institute-supported symposium on evaluation of drug therapy in neurological and sensory diseases, published this year, a special report of the panel on Parkinsonism was included. This report may serve as an outline or guide for workers in the field of drug testing and drug evaluation in different clinical centers throughout the country.

Advances have also been made in the surgical relief of involuntary movements and in the simultaneous exploration and increased understanding of the disorder itself. The development of neurosurgical techniques for the relief of Parkinson tremor began in 1937 with the introduction of excisions of the cerebral cortex in the motor and premotor areas. The surgical approach is based primarily upon partial isolation of the parts of the brain involved in Parkinsonism. This is achieved by cutting some of the nerve paths which connect these areas with the rest of the body. Another surgical approach, called spinal pyramidotomy, is not an operation on the brain but rather a relatively minor procedure for severing nerve tracts within the spinal cord.

In some instances, oil or alcohol is injected directly into special deep-lying areas of the brain. In others, a tiny radioactive substance is injected into the area, and in still other instances the areas are coagulated with an electric wire.

In one method the areas are bombarded from a distance with ultrasonic waves or proton rays.

New encouragement is given in the approach to surgical procedures since techniques have recently been designed for the objective moment by moment measurement of tremor and rigidity. This promises to be of great monitoring value during surgery, as well as an objective measurement for postoperative evaluations.

One of the difficulties complicating the surgical approach is variations among patients of the position of the brain structures, especially of the basal ganglia which lie deep within the brain. Consequently, research investigators have turned their attentions to devising instruments which will aid in the accurate location of the basal ganglia and other structures of the brain. Continuous improvements in roentgenologic, stereotaxic, and other techniques have been devised to aid the surgeon in the proper anatomical placement of the surgical lesion.

Simultaneously with advances in treatment, a better understanding of the nature of the disease is emerging. An imposing weight of evidence now implicates the basal ganglia in Parkinsonism and certain other forms of involuntary movement disorders. The basal ganglia are nuclear masses situated deep within the central part of the brain. They are important way stations having to do with the regulation of movement, the maintenance and regulation of posture, and probably the performance of many automatic and involuntary types of posturing activity. Pathological studies have demonstrated that several structures within these nuclei are affected in cases of Parkinsonism. In experimental animals, destruction and stimulation of certain of these regions may produce Parkinson-like disturbances. The neurosurgical approaches to involuntary movement are directed primarily toward these areas of the brain.

The basal ganglia have long been known to have certain unique chemical characteristics which appear to render them unusually susceptible to certain toxic agents. It is these structures which are selectively damaged in cases of neonatal jaundice. They are the primary target of intoxication with manganese. In chronic epidemic encephalitis, they appear to be a primary and highly selective target of the yet unknown viral agent. Therefore, the recent discovery that certain of the tranquilizing agents are capable of producing Parkinsonism is a development of tremendous importance.

It is quite clear that the effect of tranquilizing agents is related to interference with the metabolism of some important chemical substances called catecholamines. One substance called dopamine (dihydroxyphenylalanine) has now been demonstrated to exist in unusually high concentration within certain of the basal ganglia. It is believed that one of the actions of the tranquilizing agents is the interference with the effective utilization of dihydroxyphenylalanine. It is also postulated that the degree of activity of the basal ganglia may depend upon a balance between catecholamines and another group of hormonal agents—the acetylcholine-histamine system—which also have a regulatory effect on the basal ganglia. Disturbance of the balance between the two groups of agents may result from the administration of the tranquilizing agents. This hypothesis is being tested now by the administration of other agents known to influence the balance. It has been demonstrated in the tranquilizer-induced Parkinsonism that the administration of a drug which blocks the acetylcholine-histamine system produces a rapid amelioration of symptoms.

Studies of the toxic agents are opening up an entirely new avenue for further exploration of Parkinsonism and other forms of involuntary movement. The classification of these disorders on the basis of their chemical characteristics is already underway, and differences of the urinary excretion patterns in various types of Parkinsonism have been demonstrated. An accurate knowledge of biochemical abnormalities offers promising hope for more effective chemical control of this great affliction.

Through a large survey of phenothiazine-induced extrapyramidal reactions or involuntary movements, published earlier this year, additional observations were reported regarding the reactions of patients to tranquilizers. Correlations have been noted between the frequency of extrapyramidal reactions and the chemical structure and potency of the phenothiazine derivative used. The reactions appeared only in neurologically susceptible patients, and a close parallel was found between drug-induced and naturally occurring extrapyramidal reactions.

Through studies by Institute workers in cooperation with St. Elizabeths and Spring Grove State Hospitals, the question of hereditary susceptibility in relation to Parkinsonian reactions to tranquilizers was explored in a pilot study this year. The findings, which have been submitted for publication, suggest that there may be a hereditary susceptibility to Parkinsonism produced by ataraxic (tranquilizing) drugs.

Other investigators have been engaged in clinical and pathological studies of Parkinsonism-dementia complex, an endemic disease on the island of Guam. In June of this year, investigators reported to the American Neurological Association that their early findings suggest Parkinsonism-dementia complex and amyotrophic lateral sclerosis may be variations of the same disease. A toxic agent in the unusual diet of the Chamarro natives is under investigation as a possible cause.

Enzymatic and other histochemical studies are being pursued in two recently discovered mouse neurological mutants. These mutants have a number of symptoms of human clinical interest, such as locomotor and postural abnormalities, motion tremor, tremor at rest, and athetoid movements. Biochemical and histological studies of these mutants are being supplemented with important genetic studies. Efforts are being made to trace the neuropathology associated with the symptoms as far as possible into post- and pre-natal development in an effort to identify the site and mode of action of these mutant genes.

Similarly, grantees in Europe have been conducting clinical and pathological studies of spontaneous nervous diseases in domesticated and wild animals. They have published a report this year on studies of a series of almost 600 wild animals. Apart from studies by these investigators, relatively little has been reported on pathological findings in the nervous system of wild animals.

PROSPECTS FOR THE FUTURE

A more uniform evaluation of drugs as well as more objective evaluations of surgery are expected to yield important contributions to the solution of Parkinsonism .

As suggested by the drug evaluation panel, the probability of obtaining more effective drugs will be increased by a better understanding of the mode of action of the anti-Parkinson agents. At present the mode of action of none of the anti-Parkinson drugs is known. Closely related to this problem is that of finding a model test system in the laboratory which will permit dependable predictions of drug responses analogous to those in humans. It is also essential that further laboratory techniques be developed to detect undesirable effects of new drugs which may prevent or limit their clinical use.

The pursuit of better defined anatomical-pathological relationships in this disorder, as well as more effective technical aids in locating brain structures will be of importance to improved surgical therapy. The ideal site and size of lesion which may give maximum relief and sustained improvement is not yet clear.

The phenomenon of Parkinson-like side effects of tranquilizers appears to be a promising avenue for exploration. In drug-induced Parkinsonism, it has been postulated that the appropriate cells of the basal ganglia and their connections are reversibly poisoned by agents whose mode of action is at least partially understood. Possibly the poisons believed to exist in naturally occurring Parkinsonism and the poisonous agents in drug-induced Parkinsonism may be interfering with the same metabolic systems. Also, the question of hereditary susceptibility in relation to the side effects of tranquilizers must be clarified.

The opportunity to search for the virus which may be responsible for occasional cases of chronic epidemic encephalitis is now facilitated by the development of new methods of virus culture.

Progress in the control of this devastating disease has been slow. At the moment, palliative measures of relief are improving the outlook for the patients, but these measures are far from satisfactory. The important new prospect is for a steady, slow, increase in knowledge of the essential causes of the diseases, which will ultimately lead to prevention and control—a goal which no longer appears beyond the realm of possibility.

MUSCULAR DYSTROPHY

Mr. Fogarty. What about muscular dystrophy? Are you making any progress there?

Dr. Masland. In the general field of muscle diseases we are working on the chemistry of muscles. Muscular dystrophy is an inborn error of metabolism. That is to say, there is a specific enzyme which is lacking in the muscle of individuals with this disease. This relates to the subject of which Dr. Daft was speaking; that is, the hereditary type of disease.

Mr. FOGARTY. How does this affect people?

Dr. MASLAND. Muscular dystrophy leads to a progressive weakness, stiffening, and shortening of the muscles. It manifests itself at first by simple weakness. Then, as the weakness progresses, the muscles contract so that the individual becomes progressively crippled. Usually by the time the individual is 20 or 25 years of age, he is completely bedfast or is a wheelchair cripple.

NEUROMUSCULAR DISORDERS

Mr. FOGARTY. We have a lot of subject matter to cover yet, so we shall place your special report on neuromuscular disorders in the record.

(The special report follows:)

SPECIAL REPORT: NEUROMUSCULAR DISORDERS

THE PROBLEM

The gravity of the problem of neuromuscular ailments in the United States is difficult to assess because some of these confine the victim to a wheelchair for long periods, perhaps as much as 30 years. In others, the fatality may follow relatively soon after the symptoms appear. Deaths as reported to the National Office of Vital Statistics fail to indicate the total prevalence of neuromuscular ailments because pneumonia or some other complication may be listed as the cause of death.

Informed estimates projected from surveys indicate 200,000 persons are currently disabled with muscular dystrophy, in which the muscle tissue itself is diseased or abnormal. About 30,000 persons are disabled by disorders of the muscle-exciting system, such as myasthenia gravis and familial periodic paralysis. In a third group, with inflammation of the muscle itself known as myositis, the number affected is difficult to estimate.

However, for muscle diseases as a group, the partially disabled are estimated at 200,000, and the completely disabled at 50,000. It has been estimated that the cost in this country of partial or total care of patients with neuromuscular ailments is in the neighborhood of $150 million. (This exceeds the estimated investment in research, both private and governmental, which offers the hope for relief of this burden.) Based on a Department of Commerce productivity figure, the additional cost to the Nation in lost productivity is more than a billion dollars.

PAST RESEARCH ACCOMPLISHMENTS

The diagnosis of neuromuscular ailments formerly depended upon two major factors: The examination of the patient, including both the history of his disorder and his present state of functioning, and the family history. Neither offered a scientifically complete basis for diagnosis, because many different neuromuscular ailments produced similar symptoms, and because the role of heredity in the various disorders has not been ascertained.

Research progress has been made toward earlier and more precise diagnosis through the study of abnormalities of muscle proteins, and of serum enzymes, and through microscopic examination of a small portion of muscle tissue. Such studies involve taking a biopsy, a sample of living muscle. Some patients who have been admitted to the NIH Clinical Center with a diagnosis of incurable muscular dystrophy have been found by biopsy to have a different and nonfatal weakness of muscle.

Another new method for the analysis of muscle disorders has been made possible by the electromyograph (EMG) test. A fine electrode is inserted in the muscle and a recording made of the muscle's own electric current. This test has aided in differentiating the various neuromuscular ailments.

In the basic research field, knowledge of normal tissue has been extended by electron microscopy and newer techniques of biochemistry. Diseased tissue always must be compared with healthy tissue as a reference for alterations. For example, Institute scientists compared the cellular changes during episodes of paralysis and recovery of patients with "familial periodic paralysis." They demonstrated by both light and electron microscopy, and measured chemically, the movement of water into the cells during paralysis.

CURRENT RESEARCH DEVELOPMENTS

This past year great strides were made toward the establishment of techniques for the early diagnosis of neuromuscular disorders when scientists in California reported changes in the levels of various enzymes in the serum from patients with muscular dystrophy. In another study, grantees of the Institute in Japan found that abnormal levels of one enzyme, serum creatine phosphokinase, appeared to be specific for the diagnosis of progressive muscular dystrophy.

Studies at the Institute and elsewhere of the differential value of EMG tests are being summarized in a handbook. This text will be used for standardized diagnostic procedures in electromyography.

Developments in the field of immunology, especially in regard to autoimmune diseases, have had an impact on neuromuscular research. Preliminary results reinforce earlier predictions that myasthenia gravis might be an autoimmune disease. Grantees have determined that a constituent of serum from myasthenic patients varies in concentration in relation to the severity of the symptoms. The constituent, called serum complement, is involved in immune reactions of the blood. An abnormal globulin constituent from myasthenic patients is bound to the serum complement as well as to muscle fibers.

Institute scientists extended our knowledge of cholinesterase, an enzyme important to transmission of messages at the nerve-muscle junction. Sites of activity of the enzyme in cultured living cells of chick embryo were determined by an Institute scientist. Because anticholinesterase agents have helped to prolong the life of myasthenia gravis patients for many years, this further knowledge of cholinesterase may lead to applications in care of patients with disordered transmission of messages to the muscles.

A rare disease of muscle, called central core disease, was studied by an Institute investigator in collaboration with a group of British scientists. Studies utilizing histochemical and electron microscopic examination and biochemical study of muscle biopsy samples revealed abnormalities in both the patient and his otherwise normal father. These findings suggested that the father might be a carrier, and that more than one genetic factor must be responsible for the development of the disorder in the son.

An important advance in our knowledge may result from recent studies indicating the appearance of abnormal metmyoglobins in skeletal-muscle samples from patients with two of the four recognized forms of muscular dystrophy. The technique involved spectrophotometric absorption curves, which differed in these patients from curves in either adult or fetal normal metmyoglobin. This one technique of protein study implied that patients with these forms of muscular dystrophy have an abnormal molecular type of muscle protein, and a persistence of fetal myoglobin in the heart muscle. If true, then two forms of progressive muscular dystrophy may be "molecular diseases" similar to the inborn defect of hemoglobin in patients with sickle-cell anemia. If this implication is substantiated, the hope for successful treatment of muscular dystrophies will receive a significant impetus.

PROSPECTS FOR THE FUTURE

In spite of recent progress, much more must be learned about the structure and function of normal as well as abnormal muscles. The biochemistry of neuromuscular systems still is not understood. Much more knowledge is desired about ion permeability, enzyme actions, and muscle protein.

Progress in early diagnosis has advantages in spite of the present lack of a cure for neuromuscular ailments. Diagnosis by means of enzyme concentration tests, before symptoms of muscle weakness appear, offers the opportunity to study the purer, early defect before complicating deterioration of the muscle adds other chemical changes in the body.

Hereditary ailments are losing their aura of hopelessness as specific discoveries offer a hope for altering defective cell elements, at some future time.

MYASTHENIA GRAVIS

Mr. FOGARTY. In the case of myasthenia gravis, according to a television program I looked at the other night, this can be diagnosed and something done about it now. Did you watch that program?

Dr. SHANNON. I did.

Mr. FOGARTY. According to the program she had been given a wrong diagnosis by another doctor, and she walked out of the hospital after being given the proper treatment.

Dr. SHANNON. This girl was admitted to the hospital because of respiratory depression, an acute episode of myasthenia gravis. The problem there is maintenance of adequate oxygenation. The physician gave her morphine, which depressed respiration further, and this precipitated a crisis.

The good Dr. Casey first relieved the oxygen deprivation by putting her in an oxygen tent and actually giving her forced respiration and then gave her one of the conventional drugs that have been known to be quite effective for myasthenia gravis, one of the anticholinesterase agents. This picked her up and she went out.

He also said to her, if you recall, that she would get along as well as she wanted to because this is the type of drug that must be given on a continuing basis for a fairly long time.

I watched that show because my wife watches the program. She said that it is good. This is the first time I had seen it. I thought it was done superbly.

Mr. FOGARTY. I think it is done in cooperation with the American Medical Association, is it not?

Dr. SHANNON. It is done in association with the local physicians under the general auspices of the AMA, but they must have very good technical advice because my wife tells me that they are very precise in their portrayal of the cases.

Mr. FOGARTY. What progress are you making?

Dr. MASLAND. It is true we have drugs, a group of drugs under the term of anticholinesterases, the trade name of the most commonly used one is prostigmine. These drugs afford relief of symptoms, but they do not provide a cure which, after all, is the ultimate objective in dealing with disease. We are now beginning to establish a program for the evaluation of several forms of treatment which seem to be curative in selected instances, namely, surgical removal of the thymus gland and the use of some of the corticosteroid drugs like ACTH and cortisone.

Mr. FOGARTY. How does it affect a person?

Dr. MASLAND. Myasthenia gravis?

Mr. FOGARTY. Yes.

Dr. MASLAND. Myasthenia gravis is a form of extreme weakness which develops during continued activity. If you ask the person to hold his eyes open, at first he opens his eyes quite normally. Then in the course of a half minute or so, his eyelids begin to droop and his face will begin to flatten, and he becomes almost paralyzed. If he rests a minute or two, the muscles regain strength. It is a form of easy and extreme fatiguability.

Mr. FOGARTY. Can this happen in children?

Dr. MASLAND. It is occasionally seen in children.

Mr. **Fogarty.** I have heard of the thymus gland being removed from a child of 1 or 2 years of age because he could not breathe properly.

Dr. **Masland.** Yes.

Mr. **Fogarty.** That would not be this, would it?

Dr. **Masland.** No; it would be an enlargement of the thymus which obstructed breathing The thymus gland does seem to be involved in this.

SPEECH AND HEARING DEFECTS

Mr. **Fogarty.** What are you doing concerning speech and hearing defects? This committee has been trying to get that program off the ground for 3 or 4 years.

Dr. **Masland.** Our expenditures in speech and hearing increased over 80 percent this last year. There is a great deal of interest developing in the general field of speech and hearing, particularly because we are recognizing that many children who used to be considered retarded are actually suffering from disabilities of hearing. Not only disabilities of the ear itself, but disabilities of the perception mechanism by which they appreciate the importance and the meaning of sound.

SCREENING TESTS

So one of our most important programs is the development of effective screening tests for small children by which their hearing disability can be picked up and categorized and understood.

Mr. **Fogarty.** Where are these screening tests being applied? I think we ought to have something like that in Rhode Island.

Dr. **Masland.** They are beginning a clinic at the Rhode Island Hospital. Incidentally, at Brown University there are some very good men in basic research, Dr. Carl Pfaffman. I worked with him a number of years ago. He is doing some good basic research.

Mr. **Fogarty.** I spoke at a meeting there at Rhode Island Hospital 2 or 3 months ago. There is a great deal of interest, more interest than I have seen exhibited before. In the last couple of years more people are talking about it and want something done about it.

Dr. **Masland.** We had a group of consultants who advised us on this program this year. They said we should establish a number of centers around the country where there is a treatment and research clinic, people interested in basic research and training facilities.

Mr. **Fogarty.** This would be an excellent place, I think, because this is a teaching hospital. We have some excellent men at Brown and are going to have a medical school there. I must ask them to get their thinking caps on and get in touch with you.

Dr. **Masland.** The important thing is to recognize the defects, if possible, even before they get to school. If they can have specialized training in those early years, they may be brought to the point where they can go into the regular school.

Mr. **Fogarty.** What year?

Dr. **Masland.** Four or five.

This is an example of the type of side issue that comes up in the collaborative project. Every one of these babies is having an examination for speech and hearing at the age of 3. Then, of course, they are going to be followed until they get through the first year in school. The objective of this is to determine with accuracy the basic defect in these children, how early it can be recognized, and the types of examination effective in picking up these children at the earliest possible age.

PROPOSAL FOR SPEECH AND HEARING CLINICS

Mr. FOGARTY. Will you supply for the record what you think we ought to be doing now to establish clinics in order that screening tests can be given so that these problems can be corrected?

Dr. MASLAND. Yes, sir.

(The information follows:)

The development of a strong program for the study of hearing and language disorders can best be accomplished through the establishment of a number of university-based clinical research centers throughout the country. These centers should assume responsibility for patient care on an outpatient basis in order to have access to adequate research and training material.

They will serve as focal points for research and research training programs at the predoctoral and postdoctoral levels. The establishment of 11 such centers at a cost of $1,100,000 is envisaged in 1963.

Mr. FOGARTY. We also have a problem in the schoolroom of teachers not noticing or not being able to determine some of these problems. They go unnoticed and go for years before anything is ever done, and sometimes it is too late.

Dr. MASLAND. We have some data on this. Apparently about 7 percent of the children in the schools have a disability of understanding sufficient to be beyond the socially acceptable level.

Mr. FOGARTY. Put your full special statement in the record. We want to do something on this problem this year.

(The material referred to follows:)

SPECIAL REPORT: DISORDERS OF HEARING AND SPEECH

THE PROBLEM

An estimated 6 million people in the United States today have some kind of hearing defect. Many of these are seriously handicapped by deafness and about 125,000 are totally deaf.

The severe problems of the person with impaired hearing are often increased by the public's attitude toward him. He may be considered as either slow, inattentive, vague or overaggressive, because of a failure on the part of his associates to recognize that his behavior is the result of a communicative disorder.

In addition, congenital hearing defects in infancy may have a profound adverse effect upon the child's ability to develop speech.

Because there are so many people who are handicapped by hearing disorders, an effort has been directed toward the improvement of hearing aids, the search for better drug and surgical techniques, reeducation and rehabilitation. Also, considerable emphasis is being placed on early and better diagnosis and on the improvement of screening techniques.

There are special hearing and speech problems which are constantly increasing in the adult population; one is hearing loss resulting from injury to the hearing mechanism from exposure to an excessively noisy working environment; another is the gradual atrophy taking place in the inner ear and in the auditory cortex of the brain in the aging population. These two conditions are increasing and becoming more of a national problem as the noise level in many industries increases and as the average age of the population rises. In hearing we are also concerned about disorders such as otitis media—an infection of the middle ear—otosclerosis, conductive and perceptive hearing losses, and the interpretation of sound. Some of the speech problems include stuttering and aphasia. Aphasia may be caused by brain damage at birth or as a result of cerebrovascular accidents, or may result from psychological problems as in the autistic child. Memory failure and other higher cerebral functions are also important to the field of speech.

RESEARCH ACCOMPLISHMENTS

In the past 20 years, considerable interest has been stimulated in basic and clinical hearing and speech research and in education and rehabilitation of persons with impaired hearing and speech.

New diagnostic techniques and surgical methods have been developed; effective antibiotic drugs are now eliminating ear infections; improvements are being made in hearing aid performance; excessive noise as a cause of hearing loss is being investigated; studies are underway on congenital hearing and speech disorders and on hearing loss in schoolchildren; and rehabilitative measures are offering new hope for the deaf and speech-impaired persons.

Surgery now offers several possibilities for improvement of otosclerosis—one form of deafness. Among the most notable developments in this field is the stapedectomy operation. In this operation, the stapes (the tiny bone of the middle ear) is removed and replaced with a polyethylene tube and vein graft.

Many surgeons throughout the United States have adopted this stapedectomy technique with certain modifications. For example, an Institute grantee, who had been using a wire prothesis in a slightly different manner for several years, adapted it to the stapedectomy operation.

Another surgical technique developed earlier for otosclerosis is the stapes mobilization operation. Here, the stapes, which has become fixed, is manipulated until it moves freely and vibrates again. Unfortunately, in some cases, this structure may once again become rigidly fixed.

The fenestration (window) operation is a technique in which a new opening is produced in the inner ear, permitting sound waves to bypass the diseased bone. It may be resorted to in particular cases when the stapes mobilization operation is unsuccessful.

Tympanoplasty is being used to correct or help other middle ear disorders such as perforated eardrum, chronic otitis media and other infections of the middle ear. It is an extremely intricate and still largely experimental technique which involves microscopically controlled reconstruction of the middle ear. Antibiotic drugs used in conjunction with this type of surgery now enable control of postoperative infections.

In the field of speech, in non-government-supported research, an electronic artificial larynx has been developed for persons who have lost the power of speech because of paralysis or surgical removal of the larynx. When the instrument, the size of a small flashlight, is held against the side of the throat, the sound waves it generates pass into the throat cavity and are formed into speech by the lips and tongue. The electronically produced sound waves thus replace those normally produced by air passing over the vocal cords. This is merely one indication of nationwide interest, outside of Government, in the rehabilitation of individuals with speech impairment.

CURRENT RESEARCH DEVELOPMENTS

One of the largest research programs, in which studies of hearing and speech disorders play an important part, is the Institute's collaborative perinatal project which is correlating neurological disorders of infancy and childhood with events of pregnancy and labor.

Several thousand mothers and their babies are being studied to determine, among other things, the factors before or during birth which may be a cause of impaired hearing. Within the 15 participating institutions, children born during the study will receive careful otological examinations and any abnormalities will be correlated with factors which might be responsible.

The study has already resulted in improvement of tests for detecting the presence of infections during pregnancy which may account for some congenital deafness. Jaundice of the newborn infant, German measles during pregnancy, and diabetes of the mother are frequently associated with deafness of the infant. When such children die in early infancy, careful anatomical examinations are contributing to basic knowledge of the mechanisms causing hearing damage.

Basic research in the hearing field, conducted and supported by the Institute, covers a wide range of subjects and represents an extremely important segment of the research effort. These include studies of the circulation of the inner ear, electrophysiological studies of the entire auditory system, compensatory repair, cochlear potentials, and the pathology of congenital deafness. Other subjects of study are psychoacoustics, the cumulative effect of excessive noise, hearing aid performance, hereditary hearing impairment, mechanisms of sound transmission, auditory discrimination, electrophysiologic tests, animal audiometry, and pitch judgment.

Through Institute rehabilitation grants, studies of the perceptual characteristics of deaf and aphasic children are being conducted and factors related to lipreading and cognitive abilities of deaf children are being investigated. Other studies are concerned with visual word recognition and color-form attitudes of deaf children and with investigations of the auditory impairments of old age.

A study on communication for the blind-deaf is underway utilizing pain-free stimulation of the skin, together with an easily learnable coding system. The project is attempting to provide a cutaneous language of practical use to the blind-deaf.

A research grant has been awarded to the American Academy of Ophthalmology and Otolaryngology for the initiation of a nationwide program to study the problems related to conservation of hearing in schoolchildren. Supported jointly by the Institute and the Children's Bureau, the program has already produced significant results and shows promise of future findings of importance.

Examinations of 4,000 children have indicated that audiometric testing alone does not define some physical abnormalities of the ear which, when detected, may make it possible to predict hearing loss. This program will not only ascertain methods for testing hearing loss, but will recommend methods for medical and educational rehabilitation, and will survey State institutions for children with hearing handicaps.

In the field of speech disorders, basic research in the vocal cord and laryngeal function, aphasia, and related areas, has provided a number of leads for further development. New electronic techniques of sound analysis and of muscle activity have made possible the precise examination of the speech process. Through the technique of cineradiography (X-ray movies), it is now possible to observe the tongue, palate, and larynx during speech. Similarly, a grantee is studying the mechanism of speech through the use of models of the speech apparatus.

A number of Institute grantees have been studying the brain's function in speech, particularly the role of cerebral dominance. In these studies, investigators are exploring the possible correlations between speech and left- or right-handedness, as well as the localization of the speech process in the brain.

PROSPECTS FOR THE FUTURE

Early in Institute planning, certain speech and hearing research and training needs were outlined. At that time, strong recommendations were made which provided sound guidelines for the direction of future research and training.

The development of research in this field is adhering closely to these early recommendations and a systematic basic and clinical research program is gradually gaining ground. In addition, investigations also continue in an effort to improve various otological surgery techniques in a number of specific areas such as instrumentation (binocular operating microscope), and anethesia. The choice of anesthia, in particular, is an important area needing further study since evidence now indicates that certain commonly used local and topical anesthetic drugs may cause irreversible damage to hearing when used for middle ear surgery. One study suggests that certain agents have a direct effect on the hair cells of the organ of Corti, usually considered the end organ of sound perception. Certain antibodies which have been useful in treatment of infectious disorders of the ear are now suspected of causing new problems of hearing loss. There is an urgent need to take a closer look at this problem.

Research in the fields of speech and hearing has been conducted in relatively few institutions and on a restricted scale principally because of the lack of trained personnel. There continues to be a need for people who have had considerable postdoctoral training in the fields of chemistry, pathology, neurophysiology, neurology, otology, and audiology.

Progress has been made in filling this void since the reassessment of the teaching programs in otolaryngology in medical centers throughout the country.

This interest, initiated by the NINDB, has brought about a reorientation of the teaching and training programs of a number of medical schools. Their programs are now slowly being pointed toward turning out teacher-investigators as well as practicing physicians. The change is developing through the awarding of grants to carefully selected institutions.

Contributions resulting from training in research, in terms of outstanding research performed by trainees, may not be discernible for a number of years after initiation of a training program. However, the present training programs are expected to increase the number of postgraduate trainees in otolaryngology going into academic medicine.

The success of future research in solving the problems of hearing and speech will depend primarily upon the competence and investigative skills of the basic scientists and clinicians being trained now for careers in research.

Mr. Denton. Doctor, they are singing your praises very loudly in my part of the country. There was a small boy in the district that I represent who had epilepsy, and it was thought to be incurable. He had been everywhere and without much success. They finally told him the National Institutes of Health would be the only place that could help him.

The doctor arranged for him to go to your Institute with the understanding that he would cooperate in one of the research projects being carried out at that time. Within 2 weeks they found the cause of the trouble. Now the boy has to receive an injection every day and he is apparently cured. His father happened to be a wholesale drug salesman, and he is spreading the word around in your praise every place where they buy and sell medicine. He told me I should be talking more about the work being done by the NIH. It must give you a great deal of satisfaction to do that kind of good work. The little part I had in it gave me a lot of satisfaction.

1963 BUDGET FOR RESEARCH GRANTS

With regard to 1963, of the grants that will be requested, how many will be authorized and how many unauthorized, and how many would be under your first request?

Dr. Masland. As I understand it, the question is this: Assuming a budget of $82 million, how far down our priority list would we be able to pay?

Mr. Denton. Yes.

Dr. Masland. May I supply that for the record? I would have to study it out. I believe $82 million would pay most of our approved grants.

Mr. Denton. Would you also put the number in?

Dr. Masland. Yes.

(The information follows:)

NIH request to DHEW for NINDB 1963 budget of $82,158,000

[In thousands]

	1963 preliminary	1963 President's budget
Grants and related contracts:		
Research	$51,692	$46,421
Fellowships	2,080	1,723
Training	10,900	8,765
Total grants	64,672	56,909
Direct operations:		
Research	8,663	6,566
Collaborative studies	3,859	3,496
Training activities	75	50
Professional and technical assistance	3,000	2,300
Review and approval of grants	1,363	1,499
Administration	526	386
Total direct operations	17,486	14,297
Total estimate	82,158	71,206

With specific reference to the question as to what proportion of approved applications can be financed in research and training grants under the $82,158,000 proposal, it was estimated that we could pay about 80 percent of approved new applications for regular research grant programs.

EFFECT OF CLIMATE ON MULTIPLE SCLEROSIS

Mr. DENTON. Let us go back to multiple sclerosis. Suppose a person has multiple sclerosis in a climate like this and goes to a colder climate. What would be the effect?

Dr. MASLAND. To the best of our knowledge, this does not affect the course of the disease. This has been particularly studied in Israel. The interesting thing in Israel is that people have come to Israel from all over the world in connection with their resettlement program. The people who were born in Israel and still live there do not get multiple sclerosis, but the people who come to Israel from the cold climates continue to come down with the disease after they get to Israel. As far as we can tell, the course of the disease is just as it ordinarily would be.

Mr. DENTON. Off the record.

(Discussion off the record.)

PROBLEMS IN TREATING MULTIPLE SCLEROSIS

Dr. MASLAND. One of the difficulties in evaluating the treatment of multiple sclerosis is that the disease has spontaneous remissions, and whatever you happen to do at the time the patient is getting better you are likely to assume is responsible. For this reason we have a group now working on the establishment of criteria of improvement and the criteria of cure. We had, for example, a report a year or so ago on the use of Tolbutamide. An overenthusiastic investigator treated five or six patients; they all got better. He thought it was the Tolbutamide. Actually, this was simply the spontaneous remission.

We now know that you have to do a very carefully controlled study before you are certain of the usefulness of treatment in multiple sclerosis.

DISSEMINATION OF MEDICAL INFORMATION

Mr. Denton. Now, one last question about this little boy I spoke of. How general is the knowledge you acquired which enabled you to, should I say, effect a cure of his condition? How general is that being disseminated among the medical profession?

Dr. Masland. Generally speaking, a discovery of a cure is published very promptly. We feel that within our professional and technical assistance program we have a tremendous responsibility to establish special training programs for practicing physicians. One of the things which we are planning to establish within that program is postgraduate seminars where practicing physicians will have the benefit of the very latest knowledge in neurological diseases.

Mr. Denton. I thought, of course, the disease this little boy had was rare.

Dr. Masland. Yes, that is right.

Mr. Denton. But it is too bad other people did not know about it because his father had taken him every place before he brought him to the National Institutes of Health.

Dr. Masland. There is another problem. There are so few neurological specialists. There are in the whole country only around a thousand people who are practicing the specialty of neurology for 10 million patients.

TRAINING NEUROLOGICAL SPECIALISTS

Mr. Denton. What are you doing toward training and how much more money could you effectively spend on training more?

Dr. Masland. We have 300 people in training in neurology. Actually, we are turning out about 70 per year. This will still give us a very small number of men because our training programs at the moment are directed exclusively toward research training.

Mr. Denton. How much more could you spend advantageously in training neurologists?

Dr. Masland. In training neurologists?

Mr. Denton. Yes. You can put that in the record.

(The information follows:)

Training needs

	1963 President's budget	1963 needs	Increase
Training grants:			
Graduate	$6,696,000	$11,131,000	$4,435,000
Undergraduate	0	2,500,000	2,500,000
Traineeships	2,069,000	2,069,000	0
Subtotal	8,765,000	15,700,000	6,935,000
Fellowships	1,723,000	2,000,000	277,000
Professional and technical assistance	615,000	800,000	185,000
Total	11,103,000	18,500,000	7,397,000

TRAINING NEEDS

The recently completed survey of training needs in the neurological sciences conducted by the Institute in 1961 indicates that the need for neurologists at the present time exceeds 4,000. The number actually available is estimated to be less than 1,000. The research training grant program of the Institute comprises 300 trainees in neurology, of whom approximately 70 are estimated to complete training as advanced specialists each year. An additional 20 men are being trained each year in pediatric neurology. The present programs are directed primarily at the training of personnel for teaching and research careers.

In order to make adequate care available to patients with disorders of the nervous system, the training program could be strengthened as follows: (1) the establishment within selected medical schools of a program for undergraduate training in the neurological and sensory disease sciences (the eventual objective would be to have a focal point for research and training in neurology and the sensory diseases in every medical school so that every medical graduate can have adequate training in these important fields); (2) the continued development of the present postgraduate training and research followship programs to encourage the special training in neurology of trainees in internal medicine, neurosurgery, and psychiatry; (3) the development within the professional and technical assistance program of an active program for postgraduate training of practitioners through extensive courses, seminars, demonstration projects, and information services.

Neurology undergraduate training grants, $2,500,000

A neurology undergraduate training grant program will support the development in medical schools and schools of osteopathy of full-time teaching and research units in the neurological areas including neurology and neurosurgery, and in the sensory disease areas including ophthalmology and otolaryngology. These teaching and research units will provide the necessary framework to adequately train young physicians in the diagnosis and treatment of neurological and sensory disorders; to teach the highly complex but essential skills necessary for research and specialty practice in advanced and clinical training programs; and to integrate research experience in the preclinical and clinical disciplines associated with the neurological and sensory disease areas as a part of the medical school curriculum.

Undergraduate training grants would be awarded on a competitive basis to those institutions which can demonstrate a well-conceived plan and potential for developing or improving full-time teaching and research units in the neurological and sensory disease areas. An undergraduate training grant program would complement the Institute's graduate training grant program, and would serve to stimulate the development of neurological and sensory disease training programs in those institutions which do not yet have them.

It is expected that 50 undergraduate grants could be awarded in the neurological disease areas and 50 in the sensory disease areas in fiscal year 1963. It is estimated that $2.5 million will be required to initiate the NINDB undergraduate training grant program. This program thus would insure the adequate training of physicians in the highly complex clinical skills necessary for the prevention, diagnosis, and treatment of neurological and sensory disorders. It would also provide for the introduction to capable young people the career possibilities in full-time teaching and research.

Neurology graduate training grants and research fellowships, $15,200,000

The neurology graduate training grant program provides for the development and support of research training programs in the clinical and preclinical sciences associated with the neurological and sensory disease areas. These sciences include disciplines such as neurology, neurosurgery, pediatric neurology, ophthalmology, otolaryngology, speech and hearing, neurophysiology, neurochemistry, neuropathology, comparative embryology, physiological optics, and acoustic and light physics.

In the clinical research areas, integrated programs of research training, reinforced by advanced clinical training, are provided for young physicians who are preparing for full-time research careers in academic institutions. In the preclinical research areas, the highly complex techniques of fundamental research are made available to young scientists preparing for careers in medical research.

Graduate training grants provide funds on a competitive basis for the development and support of the research training environment, including the required teaching personnel, equipment and supplies, and for the training stipend support of selected junior and advanced fellows participating in the program. It is expected that 77 new graduate training grants, including 27 anticipated to be approved but unpaid in fiscal year 1962, could be awarded in fiscal year 1963 at a total of $4.2 million. This would mean that a total of $13.2 million would be needed to support the continuation of active graduate training grants, new graduate training grants, and the traineeship program associated with them. The neurology graduate training grant program would thus provide for the predoctoral research training of preclinical scientists in critical areas of shortage such as neurophysiology, neurochemistry, and speech and hearing, and for the postdoctoral research training of clinical and preclinical scientists in essential areas such as neurology, neuropathology, opthalmology, and otolaryngology.

Applications for research fellowships have increased in the fields of neurological research. A needed program level of $2 million would support a total program of 173 awards.

Training for professional and technical assistance, $800,000

There is a great need for a more effective utilization of research findings in the neurological and sensory disease areas. It is proposed to improve techniques to provide the latest scientific information to practitioners serving at the community level. These activities will be undertaken through direct operation of a professional and technical assistance program on a national basis, as well as sponsorship or support of seminars, consultation, and other scientific and educational activities at the community, State, and regional level. Films, filmstrips, other visual aids, periodicals, and other publications, will be made available specifically for practicing physicians. Procedures are also being developed for rapid communication with practitioners through the publication of specially prepared scientific digests.

Mr. DENTON. That is all.

EXPENDITURE OF INCREASED APPROPRIATIONS

Mr. MARSHALL. I note that in 1954 the Congress appropriated $4,500,000 for this work.

Dr. MASLAND. Yes, sir.

Mr. MARSHALL. In 1962 the budget request was for $54,100,000.

Dr. MASLAND. Yes, sir.

Mr. MARSHALL. The Congress saw fit to appropriate $70,812,000.

Dr. MASLAND. Yes, sir.

Mr. MARSHALL. Which is $16,712,000 more than the budget request of last year.

Dr. MASLAND. Yes, sir.

Mr. MARSHALL. I would like you, at this point in the record, to put in a statement to show what you spent the $16,712,000 for.

Dr. MASLAND. Yes, sir.

(The information follows:)

[In thousands]

	1962 President's budget	1962 appropriation	1962 operating plan	Increase, operating plan over President's budget
Grants and related contracts:				
Research	$35,384	$44,460	$39,126	$3,742
Fellowships	980	1,780	1,723	743
Training	7,846	10,000	8,765	919
Total grants	44,210	56,240	49,614	5,404
Direct operations:				
Research	5,744	6,621	6,455	711
Collaborative studies	2,592	3,057	2,955	363
Training activities	50	75	50	0
Professional and technical assistance	0	3,000	1,500	1,500
Review and approval of grants	1,181	1,469	1,376	195
Administration	323	350	350	27
Total direct operations	9,890	14,572	12,686	2,796
Total estimate	54,100	70,812	62,300	8,200
Unprogramed funds			8,512	
Grand total			70,812	

Mr. MARSHALL. That is all, Mr. Chairman.

Mr. FOGARTY. This is one of the more encouraging reports you have given us since you have been heading this Institute, I think.

Dr. MASLAND. Thank you.

Mr. FOGARTY. But you still have a lot of basic research to do, do you not, in all these areas?

Dr. MASLAND. That is right.

CEREBROVASCULAR DISORDERS

Mr. FOGARTY. We didn't talk much about your work in the field of cerebrovascular disorders, submit a statement on that for the record.

(The statement follows:)

SPECIAL REPORT: CEREBROVASCULAR DISORDER

THE PROBLEM

Today, cerebrovascular disease ranks third in causes of death in the United States, exceeded only by heart disease and cancer. In 1959, 11 percent of the reported national mortality was attributable to cerebrovascular disease. Recent reports indicate 21 percent mortality following an initial attack of cerebral thrombosis. Moreover, of the 79 percent who survive the first stroke, one-half die within about 4 years.

While most deaths from cerebrovascular disease occur in older persons, there are age variations among the different conditions grouped under this heading. Deaths from subarachnoid hemorrhage, for example, are more common between the ages of 40 and 60, whereas cerebral hemorrhage and thrombosis show increasing incidence with age. Of 1,800,000 victims of cerebrovascular disease alive today, about one-third are wage earners made unemployable by the residuals of a stroke.

At present, there are about 16 million people over 65 years of age; by 1970, the number will have risen to 20 million or more. Even though modern medicine may be able to provide more successful treatment than it has in the past, the problem can be expected to remain a serious one since there is a growing proportion of older citizens in the population.

A concerted attack on the problem of cerebrovascular disease is being made by the Neurology and Heart Institutes, by a Joint Subcommittee of the Councils of the two Institutes, and by groups of consultants.

Several years ago, a group of consultants under a neurology grant prepared a Classification and Outline of Cerebrovascular Diseases. This was widely distributed and research has benefited as uniform cerebrovascular terminology has gained common acceptance.

More recently, under a neurology grant, well-known scientists in the cerebrovascular field have conducted a study and produced a report on the present status of cerebrovascular disease.

The interest of both the Neurology and Heart Institute Advisory Councils in cerebrovascular disorders has been unified through a joint council subcommittee. This subcommittee has been responsible for the wide distribution of the report on the present status of cerebrovascular disease (Survey Report of the NINDB Cerebrovascular Study Group) as well as the distribution of The Transactions of the Third Princeton Conference on Cerebrovascular Diseases. This conference was supported by a grant from the neurological institute.

The subcommittee has prepared a trial cerebrovascular bibliography for use in research and teaching. The bibliography is being distributed during its developmental period to a limited number of investigators and teachers. The present plan provides for an issue every 4 months over a 2-year period. Each year one or more issues will contain a comprehensive index. The experimental bibliography was prepared with the cooperation of the National Library of Medicine and was supported by grants from Heart and Neurology. After a trial period, the publication will become generally available to scientists and others interested in this field.

RESEARCH DEVELOPMENTS

The present cerebrovascular research program of the U.S. Public Health Service is centered in two of the National Institutes of Health: the National Institute of Neurological Diseases and Blindness, and the National Heart Institute.

Neurological research activities

Research in cerebrovascular disorders has been moving forward along several major avenues. Epidemiological and various other studies have been pursued to determine the causes of these disorders. Investigations of the anatomy of the blood vessels and other structures associated with cerebrovascular disorders, as well as studies of the blood flow and circulation, are adding knowledge important to the understanding of the nature and physiology of cerebrovascular disease. Studies of clotting and additional mechanisms through which cerebrovascular accidents occur are being pursued. Other efforts are being made to perfect diagnostic measures—especially angiography. Efforts also are continuing to evaluate and improve surgical techniques and drug therapy—particularly anticoagulants and fibrinolytic agents.

Numerous studies have been conducted to discover factors that may play a role in the development of atherosclerosis. Because the observations to date have not been consistent, many suggested etiological factors have been reexamined this year in a large series of cases. This study, however, was limited to disorders involving changes in certain larger arteries—called the circle of

Willis. From this survey, it was reported that, contrary to previous beliefs, fatty deposits in cerebral atherosclerosis is a secondary process, rather than a primary event—and at times may be absent. Of all the factors studied, only two seem to play a role in the cerebrovascular degenerative process: hypertension and malignant disease. Patients with hypertension show a considerable increase in the frequency and severity of this degenerative process, while those with malignant disease showed considerably less. There is a suggestion that diabetes may hasten the cerebral atherosclerotic process, but no conclusions have been reached. In atherosclerosis, which increases in frequency and severity with age, age, contrary to previous beliefs, was considered an accompanying factor rather than an etiological agent. Age may accentuate atherosclerosis, however. Such factors as mechanical stress, endocrine disturbances, obesity or malnutrition, chronic infections, and other somatic disease appear to play very little role in cerebral atherosclerosis. The factor of race in cerebral atherosclerosis is still undetermined.

Among the several major research approaches to the overall problem of cerebrovascular disorders is the attempt to gain a clear picture of the nature of the vascular change and its location in the cerebral blood vessels. In some instances, these changes may lead to an occlusion of the blood vessel, called thrombosis; in others, the blood vessel may rupture and hemorrhage. Thus, scientists are studying both the normal structure of the blood vessels and the blood circulation, as well as the abnormal anatomical and physiological changes associated with cerebral disorders. From such an approach, scientists are learning more about certain types of pathological changes occurring primarily in the large blood vessels which lead to massive strokes.

In the area of neurovascular anatomy, comparatively few special studies had been made sporadically in the past. Now, newer techniques have stimulated more interest in this area. The recently developed angiographic techniques have provided scientists with a tool for studying the anatomy of the primary artery—the internal carotid—which supplies the anterior two-thirds of the cerebral hemisphere. Occlusions or buckling of this major vessel can result in paralysis of one side of the body (hemiplegia), speech failure (aphasia), and other seriously crippling conditions.

Similarly, investigators are gaining more information about the changes in the small vessels—the capillaries. Blockage of these small vessels may lead to very small or imperceptible strokes, and ultimately to dementia. The two processes appear to be independent.

Over the last decade, scientists have continued their microscopic explorations of the small vascular malformations which cause massive intracerebral bleeding, called intracranial hematomas. With better knowledge of these malformations and improved diagnostic techniques, it is sometimes possible to save the patient by surgically resecting the abnormal vascular network or occluding the tributary arterial circulation.

It is believed that there are differences in the extent, character and location of vascular changes in people which may be correlated with the geographic variations throughout the world. In pursuit of such a possibility, this Institute is organizing an extensive international research program for the comparisons of cerebral blood vessels, obtained at post mortem, from individuals all over the world. These studies may help explain why a given type cerebrovascular disorder is highly prevalent in one geographic area and almost nonexistent in another.

In addition, scientists are conducting histochemical studies to determine the metabolic changes underlying the thickening of the vessel wall.

Through improved histochemical staining techniques, Institute grantees have confirmed the presence of nerves in human and animal arterial tissue. These anatomical studies are important to the confirmation and elucidation of the concept of cerebral vasospasm. From these studies, preliminary evidence is also available on the morphological characteristics of the periarterial innervations of the major portions of cerebral arteries in man.

Much more is being learned about the so-called blood-brain barrier which restricts the passage of substances into the brain and spinal fluid. From previous studies it has not been determined whether the experimental dyes used to demonstrate this barrier had an affinity for particular tissues or whether there was an absence of blood-brain barrier. This year, however, scientists at the National Heart Institute have demonstrated that in special regions of the brain, the blood-brain barrier is nonexistent.

In recent years, great interest has been stimulated in the study of cerebral circulation and metabolism. Evidence has been accumulating which shows that changes in cerebral metabolism influence local blood flow and, conversely, that cerebral metabolism may become temporarily or permanently reduced when local circulation fails. Attempts have been made this year by grantees to define the regulatory and biochemical mechanism within the brain whereby increased local metabolism results in localized hyperemia (blood excess). These studies have been possible by using new recording techniques for correlating localized changes in cerebral metabolism with changes in cortical blood flow. The most important single factor in this homeostatic mechanism was local carbon dioxide production. These investigations may prove important to understanding the mechanisms involved in many physiological reactions, including vascular occlusion, cerebral ischemia, and the introduction of drugs to the vascular system.

Scientists have been limited to some degree in their studies of cerebral circulation because of several factors: (1) the brain's relative inaccessibility to direct observation, (2) its sensitivity to trauma, and (3) the difficulty of finding a method which does not interfere with blood flow necessary for the brain. Now, improved techniques for measuring blood flow in each cerebral hemisphere are expected to help expedite the further elucidation of cerebral blood circulation. These techniques involve the use of external monitoring devices of intravenous injections of radioisotopes.

The actual mechanism involved in stroke also is under investigation. Of particular interest is the so-called transient ischemic attack—a situation in which an individual with impending stroke may, for a number of days or months, have recurrent fainting or weak attacks. Research efforts are being made to determine whether these attacks represent a transient fall in blood pressure, the temporary and recurrent clotting (thrombosis) of a blood vessel, or the formation of a clot in a diseased vessel with subsequent passage to the terminal branches of the artery. Studies of the clotting mechanism, factors influencing the viscosity of the blood, and the hydrodynamics of blood flow through the cerebral vessels relate to this problem.

In examinations of the effects of hyperventilation on cerebral hemodynamics, grantees have observed a rapid response of cerebral vessels to a reduction of carbon dioxide tension. These studies prompted possible explanations for the failure of an overall reduction of cerebral blood flow to evoke evidence of localized cerebral ischemia in subjects with cerebral vascular insufficiency. Further research must be done before these suggestions can be completely tested.

In studies of cerebral dynamics in syncope, or unconsciousness, the deprivation of oxygen in small areas of the brain may be the primary cause.

From investigations of the main cerebral arteries in association with stroke, investigators have suggested that these arteries may play an important role in blood pressure regulation. The close association between high blood pressure and strokes possibly may be due to manifestations of a single condition—the reduced blood-carrying capacity of the main cerebral arteries, both extra- and intra-cranial. It is generally accepted that liability to stroke is increased very greatly by the presence of general circulatory insufficiency of any kind.

The primary objective, of course, is the prevention of vascular changes which predispose to cerebrovascular disorders. It is equally important at this time, however, to develop effective techniques for the early recognition of dangerous vascular disease. With accurate and early diagnosis, it is now possible in many instances to anticipate the occurrence of a stroke and sometimes to prevent it. Some of the techniques of blood flow measurements alluded to already, such as radioactive tracer isotopes, are helpful.

A grantee study on continuous measurement of cerebral circulation has resulted in the development of a device for quick and accurate measurement of arterial pressure in the brain. Known as the Thorner pulsenor for the ophthalmic artery, its potential clinical uses are reported to include detection of brain tumors and early diagnosis of patients prone to strokes.

Improvements in electroencephalography, arteriography, oscillometry ,and other techniques are promising to facilitate pinpointing the anatomical areas of disturbance. For example, preliminary reports indicate it may be possible to determine the site of lesion in occlusive disease of the common carotid artery by oscillometric measurements.

The electroencephalograph, long used in differential diagnosis of vascular disease, can also be of value now as an aid in localizing the involved brain area and in determining the relative adequacy of cerebral blood flow.

Most helpful as a diagnostic technique, however, is the newly perfected procedure of angiography. Using this technique, based on X-ray principles, it is possible to observe the vessels and site of lesion which could lead to strokes. Angiography has contributed immensely to surgical success in treating intracranial aneurysms and angiomas.

A simpler and more rapid technique than angiography for diagnosing the blocking or narrowing of blood vessels to and in the brain has been devised by Institute grantees and Veterans' Administration investigators. The newer technique consists of injecting radioactive hippuric acid in an arm vein while a blood pressure cuff is on the arm. When the cuff is released, the blood passes quickly through the heart-lung circulation and into the brain. The rate of blood flow through the two hemispheres of the brain is measured by two scintillation counters on either side of the head. The entire blood flow test can be completed in 45 seconds.

Advances have been made in the treatment of cerebrovascular disease primarily by the use of anticoagulants and surgery. Anticoagulant drugs are beneficial primarily in preventing the formation and propagation of thrombi, or blood clots. Thus, anticoagulants seem most effective in treatment of recurrent transient ischemic attacks and the slowly progressive stroke as well as cerebral embolism. Once infarction has occurred, however—as in the acute phases of cerebral thrombosis—anticoagulants may be of little value or possibly may be dangerous.

In view of the conflicts of medical opinion concerning the values and dangers of anticoagulant therapy in cerebrovascular disease, it is necessary that anticoagulants be thoroughly assessed. In strokes, the evaluation of this treatment is most difficult because both the occurrence of a stroke in the individual and the course of recovery are highly variable and unpredictable. The evaluation of anticoagulants has, therefore, required a vast cooperative study, now nearing completion, supported by this Institute. Simultaneously, smaller investigating teams have been attempting to assess the use of anticoagulants.

Meanwhile, a new anticoagulant, thromboplastinase, appears very promising. because it strikes selectively at the earliest phases of coagulation, it may have greater usefulness than current drugs in preventing clotting. This drug—an enzymatic material—acts by destroying thromboplastin and thus barring conversion of prothrombin to thrombin.

Scientists are turning their attention to other drugs, such as thrombolytic and fibrinolytic agents, which may offer hope for prevention of clotting, and the enzymatic dissolution of firm intravascular clots. To be useful, these agents must be effective in dissolving the fibrin which binds the clot without affecting adversely the other proteins in the blood and without producing adverse side reactions. In some studies, plasmin is injected into the circulatory system to increase fibrinolytic activity.

In general, results from thrombolytic therapy have been encouraging, and promise to be effective adjuncts to surgical removal of thrombi and emboli. However, much more research is needed for the clinical correlation of laboratory tests, the determination of appropriate dosage recommendations, and the elimination of undesirable side effects.

Advances also have been made in surgical techniques for certain cerebrovascular disorders. Of particular interest is a form of stroke which occurs secondary to cerebral aneurysm. In this condition there is weakening of the vessel wall followed by its sacular dilation, eventual rupture, and, frequently, fatal hemorrhage. The sacular dilation, or aneurysm, may now be demonstrated by angiography. Surgical removal is feasible in some instances. The Institute has organized a cooperative study at times involving as many as 20 institutions to determine precisely which types of aneurysms are suitable for surgical intervention and which are more effectively handled by medical procedures such as sedation and reduction of blood pressure.

New surgical aids which include the use of hypothermia are improving the results of the operative approach. Under conditions of hypothermia, the brain metabolism and its need for oxygen are significantly reduced. This permits the cerebral circulation to be interrupted for long periods of time during which the diseased cerebral artery can be excised or repaired.

Broad, multifaceted, and long-range approaches to the clinical problems in cerebrovascular disease are being made possible through Institute grants for the establishment of three cerebrovascular research centers. At these institutions—Cornell University, Wayne State University, and the University of Minnesota—research teams already having distinguished records for their work in this disease area, will intensify and expand current research programs in a coordinated manner.

The cerebrovascular research center at Cornell University will provide for research on the natural history of the disease, improved methods of diagnosis, treatment with particular emphasis on anticoagulant and surgical therapy, the clotting mechanism, the role of the thrombolytic mechanism and thrombolytic agents, and the role of lipids in the pathogenesis of cerebrovascular disease.

At Wayne State University, the cerebrovascular research center will be concerned with such studies as lipid metabolism in cerebrovascular disease, pathogenesis of cerebrovascular symptoms, the nature and treatment of cerebral accidents—especially hypertensive hemorrhage, encephalopathy, cerebral aneurysms, and anticoagulant and fibrinolysin therapy, arteriographic studies, cerebral blood flow, and cineangiographic studies.

Research at the University of Minnesota Cerebrovascular Research Center will embrace such areas as the anatomy and pathology of cerebral vessels; the etiologic factors in cerebral atherosclerosis; the physiology of cerebrovascular disease, including cerebral blood flow studies; the central nervous system effects of congenital heart disease; cerebrovascular insufficiency; subarachnoid hemorrhage and cerebral aneurysms; oxygenation and nutrition of the brain; exploration of the blood brain barrier; and aphasia, or speech loss, in stroke patients.

Other multidisciplinary research centers are being established through Institute grants, dealing with a number of disease categories in neurology, which are expected to contribute significantly to the solution of this medical problem. Such centers include a neurological clinical research center at Albert Einstein College of Medicine, special clinical research projects in neurophysiology at the University of California, and a neurological research center at Columbia University.

National Heart Institute activities

The research attack on cerebrovascular disease includes many of the Heart Institute's conducted and supported studies concerned with atherosclerosis and hypertension. Among these are studies concerned with the general problems of pathogenesis, disease processes, and mechanisms; subject areas such as anticoagulants, fibrinolysis, diet, hormones, and many others; and studies relating to special aspects such as cerebral angiography, vascular surgery, and cerebral circulation.

Of special significance is a cooperative study presently in progress on cerebral arterial insufficiency, in which some 16 geographically dispersed investigative teams are participating. In the past few years it has become recognized that atherosclerotic disease of extracranial arteries supplying the brain can produce significant cerebral symptoms. It has also been shown that surgical treatment of well-defined atherosclerotic lesions in such arteries located in the neck and upper chest can dramatically restore adequate cerebral blood flow. In the cooperative study, patients with symptoms of cerebral insufficiency are studied by angiography and other diagnostic methods to determine whether impeded blood flow in extracranial arteries is the principal cause of the symptoms. Those patients who are found to have occlusion of extracranial arteries and considered likely to benefit from surgery are treated by the most appropriate surgical procedure to remove or bypass the impediment to blood flow. All of these patients are intensively studied before and after treatment under a standard protocol, and the data obtained are being pooled in a central registry at Baylor University for analysis. Results of this 5-year study, when completed, should provide information on a number of important aspects. It is expected to meet the need for better criteria by which to select patients suitable for surgical treatment; provide knowledge of the effects of such arterial surgical treatment; provide knowledge of the effects of such arterial surgery on cerebral blood flow; and provide patient evaluation data for determining the clinical benefits of such surgery and, perhaps, what the optimum form of treatment may be.

Complementing the efforts being made in research, the application of knowledge to benefit the stroke patient is also being extended. Grants and technical assistance provided to States under the heart disease control program are helping to accelerate community activities in this field. More than a dozen States are now allocating part of their grant funds for cerebrovascular disease programs. Areas of activity and emphasis vary in different States but commonly include professional education, demonstration and research projects, and methods evaluation.

In Georgia, a notable program of restorative services for stroke patients has been developed that involves participation of the State health department, heart association, medical schools, and medical societies. Hundreds of public health nurses have been trained in proper bed positioning and exercises necessary to restore function in stroke patients. They can thus bring recommended rehabilitation procedures to patients in their homes, with the result that much disability is prevented. In Pennsylvania, a stroke program conducted in one county includes education of professional workers and of the public, home care of stroke patients, and full use of community resources; in addition to a county stroke rehabilitation program, a project is being undertaken in cooperation with a Portland hospital to diagnose those patients with cerebral insufficiency and partial arterial occlusion who might benefit from surgery. In Colorado, a rehabilitation program for stroke patients is being conducted and a program is being developed for the detection of patients with cerebral insufficiency with a view to preventing strokes.

The stroke programs in these and other States are encouraging evidence of progress in a field where only a few years ago very little except pioneering was being done. Also, the former disheartened attitude of the public concerning cerebrovascular disease and strokes has begun to give way to some degree as research developments are made and become known. Information-education activities, including pamphlets such as the Heart Institute's "Cerebral Vascular Disease and Strokes" and the Neurology Institute's "Little Strokes," have helped to spread understanding of these conditions and the knowledge that it is possible to do something for many of those afflicted. Another publication, "Strike Back At Stroke," prepared by the Public Health Service's Division of Chronic Diseases and endorsed by the American Medical Association has proved exceedingly valuable. The booklet, now in its third printing, shows in words and pictures how the stroke patient can be helped at home by performing exercises designated by his physician to restore him to self-care and independent living. The publication has been used by stroke programs in professional education activities as a manual of effective rehabilitation techniques and by many individual physicians as a specific prescription for therapy to be carried out by the patient and his family.

PROSPECTS FOR THE FUTURE

The new possibilities for therapy carry with them difficult and sometimes hazardous diagnostic procedures demanding specialized skills. Since very few clinics in the country have personnel trained in these procedures, one of the future needs is the training of personnel in these new diagostic methods and in surgical techniques.

Surgeons have made rapid and dramatic advances in the treatment of patients with occlusive vascular disease in the upper chest and neck. Perhaps future research will discover new ways of modifying brain circulation. At present, even those individuals who have occlusive disease in the vertebral canal are not surgically approachable.

A precise knowledge of the role of anticoagulants may require a more accurate understanding of the clotting mechanism. Pathological examination of diseased cerebral arteries is revealing the existence of arteriosclerotic plaques and of small neural thrombi. The recurrent formation and subsequent release of many such thrombi, or clots, may account for recurrent minor vascular attacks and loss of consciousness in some patients.

The future should reveal more knowledge about atheromatous and thrombotic processes, both physiologically and chemically. Fortunately, these areas are now being explored in a number of clinics. Preliminary clinical results from thrombolytic therapy have been encouraging and promise the development of a practical and effective adjunct to surgical removal of thrombi.

Mr. FOGARTY. Is there anything else you would like to say?

Dr. MASLAND. No, sir.

Mr. FOGARTY. Thank you very much.

Dr. MASLAND. Thank you, sir.

(The following was submitted for the record at the request of the committee:)

DEATHS, DISABILITIES AND COST OF NEUROLOGICAL DISEASES AND BLINDNESS

NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS

Statistics of the annual number of deaths and total current number of disabilities caused by each of the major diseases handled by the National Institute of Neurological Diseases and Blindness, and the estimated annual cost to the Nation.

I. Deaths from neurological ailments during 1959 (National Office of Vital Statistics)

Category:[1]	*Number*
Cerebral palsy	1,268
Cerebrovascular diseases (includes strokes and related brain ailments)	191,376
Parkinson's diseases (paralysis agitans)	2,924
Multiple sclerosis	1,389
Muscular dystrophy and related ailments	585
Epilepsy	2,069
Myasthenia gravis	209
Amyotrophic lateral sclerosis	1,011
Encephalitis	570
Brain tumors	4,705
Total, by reportable categories[1]	206,106

[1] The approximately 200 different neurological ailments pose unusual statistical problems. The cerebral palsy figure above includes categories 351 and 352 of vital statistics but not the cases found in the undifferentiated "other" of 334 of vital statistics. Mental retardation, blindness, deafness, and speech disorders are major problems in neurology, but are not immediate causes of death. Even in the ailments for which deaths are reported, figures are unreliable because the chronically ill patient, weakened by disease, may die from an intercurrent infection and the death certificate may not record the basic neurological illness.

II. Disabilities from neurological diseases

The U.S. National Health Survey estimates, from interviews at homes, that 220,000 persons consistently suffer some limitation in living because of headache or migraine. About 587,000 persons whose corrected vision is not good enough for reading newsprint are handicapped in living. As the U.S. National Health Survey does not have figures on disabilities from specific neurological diseases, this Institute uses morbidity estimates from the respective voluntary associations stemming from known experience with cases or from surveys of a given area. Some neurological patients, such as epileptics, conceal their illness to avoid job discrimination.

Total current number of disabled persons (estimated)

Disability category:	
Cerebral palsy	550,000
Mental retardation (3 percent of the population) (126,000 born annually)	5,400,000
Cerebrovascular diseases	([1])
Parkinson's disease	500,000
Sclerosing disorders:	
Multiple sclerosis	250,000
Other demyelinating diseases	250,000
Muscular dystrophy	200,000
Epilepsy	1,500,000
Myasthenia gravis	30,000

See footnotes at end of table.

Total current number of disabled persons (estimated)—Continued

Disability category—Continued	
Amyotrophic lateral sclerosis	30,000
Infectious neurological disorder (including encephalitis)	(2)
Brain tumors	(3)
Disorders of vision:	
Legally blind	350,000
Partially disabled	1,892,000
Disorders of hearing: [4]	
Totally deaf	125,000
Disorders of speech interfering with normal development	(5)

[1] Between 1,000,000 and 1,800,000.

[2] Over 1,000,000.

[3] Over 500,000.

[4] Over 3,000,000 with major hearing and speech defects, losing between 2,000,000 and 3,000,000 man-hours per day to industry.

[5] 2 to 5 percent of all children between the ages of 5 and 20.

III. Estimated annual cost to the Nation

Statistical overlapping occurs with persons who have had a stroke and are blind, or totally deaf; or who have Parkinson's disease and blindness; or with other combinations of neurological and sensory ailments.

With estimated exclusions for duplication, the total of neurologically disabled persons is more than 10 million. Of these, approximately one-third are totally disabled. It has been estimated that the cost of care for the totally disabled and for a significant number of the partially disabled is more than \$5½ billion. Lost productivity to the Nation caused by these disorders may amount to as much as \$38 billion.

The annual cost to the States of the 195,000 mentally retarded persons in State institutions is estimated at \$250 million. No one knows the cost of supporting those in private institutions. Less than 4 percent of the 5 million mentally retarded are in institutions, public or private; the cost to individual families and communities for the other 96 percent is unknown.

During fiscal 1961, the Bureau of Old-Age and Survivors Insurance paid disability benefits totaling \$60 million to 113,000 beneficiaries whose disabilities had begun in childhood. Of these disabled beneficiaries, more than 90 percent had neurological disabilities.

The Veterans' Administration paid, in fiscal 1961, \$384,490,152 to 423,379 veterans with neurological ailments.

Highlights of Progress in Research on Neurological and Sensory Disorders—1961

INTRODUCTION

The research developments discussed in the following pages represent some of the major achievements in laboratory and clinical investigations directed to the central nervous system, the brain and cerebral cortex, chronic neurological disorders of infancy and childhood, neuromuscular disorders, amyotrophic lateral sclerosis, epilepsy, and disorders of vision, speech, and hearing.

The items reported here have appeared during the past year as published papers or have been presented as scientific findings before medical groups.

CENTRAL NERVOUS SYSTEM

NINDB studies provide first evidence that nerve axon membranes have fixed electrical charge

By observing the movement of "tagged" substances across the membrane of the giant axon of the squid, NINDB investigators have obtained the first biological evidence that a nerve membrane at rest has a fixed, negative electrical charge. In general, this conclusion is based on the finding that the outflow of negatively charged ions is much slower than the outward movement of positive ions.

The permeability of the squid axon membrane to radioactive tracers was investigated under various experimental conditions by Drs. I. Tasaki, and C. S. Spyropoulos of the Laboratory of Neurophysiology, NINDB, and Dr. T. Teorell, Special Consultant (Professor of Physiology, Uppsala University, Uppsala, Sweden). Tracer substances, which were injected intracellularly, included radioactive potassium, sodium, and calcium (positive ions), chloride, sulfate, and phosphate (negative ions); and water. These elements constitute the major inorganic components moving normally across the membrane and are thought to play important roles in the normal functioning of the axon.

When the nerve axon was at rest, the average outflow time of the negative ions was found to be greater than 50 hours. In contrast, intracellular water was lost from the axon in less than two minutes, calcium in 30 minutes, sodium in less than 3 hours, and potassium in under 8 hours. This fact suggests strongly that the nerve membrane contains an electrical charge which holds negatively charged substances practically immobile. The values for sodium and water were similar to those reported by other investigators previously.

As was previously known, when the axon was repetitively stimulated, the movement of the positively charged tracers was accelerated. However, the negative tracers remained unaffected by these conditions, suggesting that the membrane remains negatively charged during activity.

The authors caution that the electrochemical force which drives the radioactive tracers across the nerve membrane is different than that which drives the corresponding nonradioactive substances. It is interesting to note that the hypothesis that biological membranes have fixed charges was proposed many years ago by Dr. L. Michaelis and by Dr. Teorell.

This study was reported in the American Journal of Physiology.

Damaged sympathetic peripheral nerves in mammals found to regenerate selectively

Studies conducted by NINDB investigators suggest that peripheral nerves regenerate selectively to appropriate nerve endings rather than randomly toward any termination. Thus, specificity of nerve fiber and nerve ending, which has been demonstrated previously in lower animals and embryos, can also be assumed to occur in adult mammals.

These conclusions resulted from studies conducted by Drs. Lloyd Guth and Jerald J. Bernstein, Laboratory of Neuroanatomical Sciences, NINDB. In initial experiments, the cervical sympathetic trunk of the cat was severed and allowed to regenerate. In normal cats, certain of the fibers connect with ganglion cells that control the dilation of the pupil of the eye; others connect with ganglion cells that constrict blood vessels in the ear. After regeneration was complete, the investigators stimulated the nerve fibers controlling these functions. They found that the original relationships had been established, indicating that regeneration had indeed been selective.

In additional experiments, they interrupted only those fibers controlling pupillary function. Before complete regeneration, the function of thees nerves is taken over by the other fibers via collateral connections. After completion of regeneration, however, the investigators found that the collateral fibers became inactive and the regenerated fibers again established appropriate connections with their original ganglion cells.

These findings were reported in Experimental Neurology.

Sensory nerve centers in thoracic wall may help regulate rhythm of breathing

An additional sensory pathway by which the rhythm of breathing is regulated has been suggested by NINDB grantees, who have found that single nerve fibers entering the spinal cord exhibit electrical activity synchronous with breathing rhythms. They conclude that numerous nerve terminals within the thoracic (chest) wall, which send signals to the spinal cord are activated at each inspiration and expiration.

Although extensive studies have been conducted to identify sensory signals arising from the lungs, little is yet known about the activity of nerve terminals lying within the thoracic wall. However, peripheral nerve centers discharging into the central nervous system are thought to influence the rhythm of breathing.

The present investigation was conducted by Drs. A. A. Siebers and E. Puletti, Medical School, University of Wisconsin, Madison, and was reported in Science.

In experiments conducted on cats, simultaneous recordings were made of breathing and of the activity of single nerve fibers in dorsal roots entering the thoracic segments of the spinal cord. Findings showed that the electrical activity of these fibers varied in frequency and in phase relationship to the respiratory cycle. Although the activity of individual fibers varied, most could be classified as either inspiratory or expiratory. In addition, the pattern of activity in a single fiber was usually similar from breath to breath.

To establish that the nerve centers sending signals to the spinal cord were not located in the lung, the investigators removed a lung from a cat and found that the signals were unchanged. Moreover, cats given drugs to cause respiratory paralysis showed neuronal activity proportional to the degree of lung inflation or deflation. Although these nerve centers were localized in the lateral wall of the thorax, the authors suggest that other peripheral nerve centers concerned with respiratory control may be located in the diaphragm, the abdominal wall, and elsewhere.

Role of nervous system in inflammatory reaction of human skin clarified

A newly defined neurohumor which dilates blood vessels, labeled "neurokinin," has been associated with the inflammatory reaction which accompanies human skin injuries. Comprehensive studies by NINDB grantees suggest that neurokinin, released from nerve endings during neuronal excitement, is the principal mediator of blood vessel dilation in such injuries. In addition, the nerve pathways responsible for redness or "flare" in injured skin are defined.

Tissue fluids collected from a site of skin injury during "flare" produced redness and severe pain when reinjected in other body areas. Tests of these fluids led to the isolation of neurokinin, a potent hypotensive and vasodilator, different from previously identified body compounds. The activity of neurokinin was enhanced by stimulation of certain nerves, but not by increased blood flow. Further work is underway to define its chemical structure more exactly.

These findings were reported by Drs. Loring F. Chapman, Armand O. Ramos, Harold G. Wolff, and Helen Goodell, B.S., of the New York Hospital-Cornell Medical Center, in the *Archives of Neurology.*

First mathematical description of heart rate reflex achieved by grantee

The mathematical description of the reflex control of heart rate through respiration has been determined by Manfred E. Clynes, Chief Research Scientist at the Rockland State Hospital, Orangeburg, N.Y. The investigation established that nerve impulses from at least two different stretch receptors in the chest are sent to the brain, in turn causing nerve impulses from the brain to the heart to be modified in a manner that could be accurately described by the derived equations. Analysis indicated that it is the stretch receptors and not blood flow changes which are responsible for initiating the rate changes.

The mathematical equations were derived from experiments in which the heart rate reflex process was duplicated on an electronic computer. The computer was fed information about the respiration of the human subject in the form of electrical signal proportional to the chest circumference—as an indicator of respiration. After many trials and analyses, mathematical equations were incorporated in the computer which enabled it to calculate the heart rate from beat to beat, under a wide variety of conditions. Close correspondence of the calculated, with the actual, recorded heart rate proved the validity of the equations describing the phenomenon .

In conjunction with studies of the respiratory heart rate reflex, as well as studies of pupillary reflex to light. the tactile information system and the carotid sinus baroceptor, the author proposed a theory based on the ability of many biological systems to respond to changes of stimulus in one direction only—called unidirectional rate sensitivity. A result of this characeristic of biological structure is that it produces patterns of behavior that have hitherto lacked explanation—the respiratory heart reflex, for example.

He concludes that while it is possible that the characteristics related to unidirectional rate sensitivity may not apply to all biologic systems, they do, like the physical laws of motion, help ascribe causative behavior to complex patterns of observation.

The results of the heart rate study were reported in the IRE Transactions of Medical Electronics and the more general aspects of biological control were presented at the meeting of the New York Academy of Sciences.

Congenital defects and endemic goiter studied in isolated New Guinea population

A recently-discovered, isolated, and still Neolithic population in New Guinea, in which many natives suffer from huge goiters and congenital nervous system damage, has been surveyed by an NINDB scientist. A preliminary report indicates that this population may provide important clues regarding the multiple genetic and environmental factors underlying these defects and the possible associations between them. The possibility that an unusual food staple may have goitrogenic action is also being investigated.

In a paper presented to the Pacific Science Congress, Honolulu, Dr. D. Carleton Gajdusek described the epidemiological aspects of endemic goiter and associated conditions in the environmentally and genetically isolated society. Located in the interior Highlands of Netherlands New Guinea, the primitive group possessed no contact with the civilized world until 2 years ago. Metabolic and biochemical studies of the population will be reported subsequently by Dr. Gajdusek.

Most of the 2,000 to 3,000 inhabitants of the region were found to suffer from varying degrees of congenital nervous system damage, ranging from slight intellectual impairment to extreme forms of cretinism and congenital deafness. In addition, endemic goiter was estimated to affect one-quarter of the males and two-thirds of the females, and in some areas afflicted all of the female population. Many of the goiters were among the largest ever reported, reaching the size of an American football. Retarded neuromuscular development, as well as mental retardation, was clearly defined in many infants.

Preliminary studies have revealed no remarkable deficiency of iodine in the soil or water of the region. However, the soil is so poor that the staple food, the sweetpotato, is of poor quality and the natives are accustomed to preparing and eating the leaves of the plant. The possibility that this food may have a goitrogenic action in the already nutritionally poor community is now being investigated.

New evidence adds to theory that certain cells regulate blood flow to neurons

Oligodendrocytes, which are enclosed in the web of tissue supporting nerves (neuroglia), were previously thought to regulate the metabolism of nerve cells and myelin.

Dr. Jan Cammermeyer, Laboratory of Neuroanatomical Sciences, NINDB, however, has observed the tendency of oligodendrocytes to cluster exclusively along blood vessels and near neurons of both gray and white nerve tissue. He theorized that the unique arrangement and strategic location of these cells might enable them to control vascular diameter and blood flow in some regions of the central nervous system. This theory was substantiated by recent findings of other investigators that oligodendrocytes connect with neurons by means of delicate nerve fibers and synaptic contacts, and exhibit a rhythmic contractility suggesting a dynamic function.

Recent observations by Dr. Cammermeyer have shown that the arrangement of oligodendrocytes varies considerably in different areas of the brain and in different mammalian species. Knowledge of the normal variations is paramount for a correct interpretation of pathologic changes. This variability may also indicate that the extent of blood flow control by the oligodendrocytes is adjusted to the needs of both individual neurons and regions, thus insuring the most economical distribution of blood.

An interesting correlation was found between the distribution of oligodendrocytes and the location of areas of brain damage. Certain disease processes which interfere with the local blood supply appeared in some instances to affect areas rich in oligodendrocytes; in other instances, areas with few of the cells were damaged. Therefore, the arrangement or content of oligodendrocytes may contribute to the variations in susceptibility of the gray and white matter to either anoxia or toxic agents, as well as to the unique localization of certain disease processes.

As a consequence of these studies, new leads for future research have been suggested. Further investigations may concern the complex of factors which may activate these groups of cells, as well as the mechanisms by which they may regulate blood flow. The studies were first presented at the Seventh Conference on Microcirculatory Physiology and Pathology. Subsequent work appeared in the *American Journal of Anatomy.*

BRAIN AND CEREBRAL CORTEX

Early effects of alpha radiation on brain demonstrated in NINDB study

Clues to a hazard man may encounter in outer space travel may be provided by an NINDB study which uses sensitive new methods to show the early effects of alpha radiation on the brain. Results in rats indicate that alpha-particle energy primarily affects brain tissue at the cellular level and the blood vessel permeability disturbance is secondary. Previous studies by other investigators have resulted in differing opinions concerning the primary site of radiation injury.

Alpha particles from the 60-inch Berkeley cyclotron were used to irradiate the dorsal surface of the rat cerebrum and cerebellum. The study was conducted by Drs. Igor Klatzo and Jaime Miquel, Surgical Neurology Branch, NINDB, Dr. Cornelius Tobias, Donner Laboratory, University of California, and Dr. Webb Haymaker, formerly of the Armed Forces Institute of Pathology, Washington, D.C.

The earliest disturbance in vascular permeability was observed at 48 hours after irradiation. A new fluorescein labeled protein technique which provides microscopic evidence of the extravascular penetration of serum proteins into tissues was one of those used. Fluorescein labeled albumin was detectable in the brain tissues for some 36 days after exposure.

However, the investigators were able to demonstrate the presence of sugar (glycogen) granules in the cells of exposed brain areas considerably earlier, i.e., within 12 hours after irradiation. Histochemical techniques showed that the glycogen was located predominantly in the glial cells. The authors suggest that radiation injury may disrupt the protein bonds of tissue glycogen, resulting in its liberation and subsequent uptake by the glial cells.

The results of the study were presented at the Symposium on the Effects of Ionizing Radiation on the Nervous System, sponsored by the International Atomic Energy Agency in Vienna, and at the 37th Annual Meeting of the American Association of Neuropathologists.

Technique reported by NINDB grantees may be useful in localizing brain injuries

A study of changes in the "steady" electrical activity accompanying brain damage may provide a new technique for determining the extent and location of damaged brain tissue.

Previously, investigations of the electrical activity of the brain have relied upon the recording of fluctuations of the electrical charge upon its surface. The record of these fluctuations, called the "electroencephalogram," has proven useful in diagnosis. NINDB grantees at Washington University have now developed a technique for recording "steady potentials" from the brain. They have discovered that an area of brain injury causes a change in the voltage which may be recorded from the surface—the injured area being maintained at a constant negative potential as compared to the uninjured part of the brain or to some common reference point elsewhere on the body.

Their most recent investigation is concerned with an evaluation of the accuracy with which a recording of these "steady potentials" can be used to delimit an injured area. For this purpose, a comparison was made of the electrical changes observed following experimental occlusion of the middle cerebral artery, changes noted after surgical excision of brain tissue, and those after localized freezing of the cortex.

Sharply defined areas of damage, such as those produced by dissection, were most sharply delineated. However, even in injuries in which the line of demarcation between damaged and undamaged tissue is less clear, such as those caused by the arterial occlusions, comparisons of relative electrical activity often indicated the boundaries of the injury and the most severely damaged areas. Thus, the technique evidently has considerable value in delineating the extent of brain dysfunction produced by various types of organic damage. These studies were conducted by Drs. Jose B. A. Keating and Warren H. Kempinsky, and are reported in *Electroencephalography and Clinical Neurophysiology.*

Brain malformations due to prenatal X-irradiation studied by NINDB grantees

A study of NINDB grantees has defined in detail the pathological changes in the brains of adult rats subjected to X-irradiation during prenatal life. Results indicate that animals exposed to radiation late in gestation survive birth and attain maturity, but develop a variety of brain defects which have counterparts in certain "spontaneous" congenital malformations of the brain in man. Nervous system defects were rarely found in rats exposed early in gestation, and radiation in the midstages of fetal development was always lethal.

Although the immediate and early effects of prenatal irradiation have received much scientific attention in recent years, long-term, enduring lesions in animals which survive to maturity and old age have been studied by few investigators. In the present study, X-irradiation was administered to pregnant rats at a specified period of gestation in a single dose of 250 roentgens. Post mortem observations were made on a total of 270 offspring, ranging from about 3 to 20 months of age at the time of death. These observations indicated that the severity and types of cerebral malformations were clearly dependent on the time of gestation at which the embryos and festuses had been exposed.

Rats which had been exposed in approximately the third trimester were reared without difficulty to adulthood and were found to have a variety of developmental malformations of the brain. The most obvious defects were a greatly diminished size of the cerebral hemispheres and skull and a pronounced decrease in brain weight. All of the malformations appeared to result from disturbances in embryological development, and were marked by a lack or decreased number, an abnormal organization, or a spatial displacement of nerve cells and their processes. One type of striking malformation not previously described consisted of an abnormal "interhemispheric" extension of the third ventricle.

These experiments are part of a larger study of the long-term effects of prenatal X-irradiation in rats. They were conducted by Drs. David Cowen and Lester M. Geller of Columbia University and the Neurological Institute of the Presbyterian Hospital, N.Y., and are reported in the *Journal of Neuropathology and Experimental Neurology.*

Studies of experimental catalepsy suggest new pathways in brain

The function of a subcortical brain center known as the caudate nucleus has been clarified by NINDB grantees who were able to obtain prolonged stimulation of the ganglion by injections, of alumina cream, which was then found to cause symptoms of catatonia in cats. About a week after injection, the animals showed no spontaneous movements, failed to eat, and responded only slightly to pain, noise, or visual stimuli. However, the cats exhibited increased respiration and heart rates and oscillatory eye movements, suggesting reflex connections to lower levels of the central nervous system.

The syndrome of catatonia was found to develop in spite of surgical removal of the frontal lobe and motor cortex, indicating that this system may not be involved. However, damage to the amygdala, an important subcortical center, was effective in preventing the syndrome. Thus, the authors conclude, the amygdala may be an important link in the system of impulses that elicit the catatonia. Inhibitory impulses from the caudate nucleus may induce the syndrome by way of the amygdala and its descending connections to brain stem centers.

Electrical recording from other brain areas showed that continuous stimulation of the caudate nucleus caused an increase in electrical discharges from the amygdala and the hypothalamus, both important subcortical centers for sensory and motor integration. This and other findings indicate that impulses from the caudate nucleus may act, on one hand, upon the motor cortex, and on the other hand, on the higher parts of the brain stem.

The study was conducted by Drs. E. A. Spiegel and E. G. Szekely, Temple University School of Medicine, Philadelphia, and was reported in the Archives of Neurology.

Relationship between two parallel metabolic pathways in brain clarified

Factors which may govern the channeling of metabolic activity via either of two parallel chemical pathways in the brain have been defined by NINDB scientists. The availability of a specific coenzyme appears to influence the probable reciprocal relationship between a direct metabolic route, by way of succinyl coenzyme A, and a "shunt" pathway, via gamma-aminobutyric acid. Previous studies by these investigators have shown that derangement of the latter pathway is intimately associated with the development of epileptic seizures.

In conducting the study, a specific phase of cerebral oxidative metabolism was investigated in subcellular bodies, known as the mitochondria, in the cat brain. Findings were reported by Drs. Guy McKhann (now of Massachusetts General Hospital) and Donald B. Tower, Laboratory of Neurochemistry, NINDB, in the Journal of Neurochemistry.

Experiments revealed that an increase in the level of the common chemical precursor, alpha-ketoglutarate, enhanced the activity of the direct pathway and depressed the shunt or gamma-aminobutyric acid pathway. However, chemicals which blocked the direct route caused an increase in the activity of the shunt pathway, indicating that high levels of the common precursor per se are not a regulatory factor.

When the mitochondria were made permeable to a coenzyme, diphosphopyridine nucleotide (DPN), the investigators found a signficant increase in the utilization of the gamma-aminobutyric acid pathway. They suggest that the two pathways may compete for oxidized DPN and that the availability of the coenzyme may be an important factor in regulating metabolism.

Computer studies suggest that brain rhythms may be basis for some behavior

Studies by NINDB grantees suggest that discriminative behavior or judgment may be based on the activity of brain waves in a subcortical area known as the hippocampus. Although the investigators emphasize that relationships between physiology and behavior are elusive, data from electronic computers showed consistent correlations between brain wave patterns and behavioral situations involving judgment in trained cats.

Data reducing and computing techniques were applied to the brain wave records taken from cats during training in T-maze approach and delayed response tests. Cross-correlations of these records showed that brain wave patterns were highly consistent in different correct trials on the same and different days. Incorrect responses were characterized by a markedly different pattern, but were also consistent.

The study, reported in Experimental Neurology, was conducted by Drs. W. R. Adey, D. O. Walter, and C. E. Hendrix, University of California, Los Angeles.

Infant monkeys found to regain motor function after removal of half of cerebral cortex

An early recovery of marked degree has been observed in infant monkeys subjected to hemidecortication (removal of the cortex of one brain hemisphere), while older monkeys retained persistent and severe deficits.

In studies conducted by Dr. Max Ramirez dé Arellano of the NINDB Laboratory of Perinatal Physiology, Puerto Rico, the neurological status of two groups of monkeys subjects to hemidecortication was determined. One group was made up of animals from 6 to 22 days old, and the other group, over 19 months of age.

Early and complete recovery from paralysis occurred in the young. The operation produced remarkably little or no facial asymmetry in the younger group, while asymmetry was marked and persistent in all of the older animals. In the younger animals, voluntary grasp reflex normalized in between 40 minutes and 9 days after surgery. Return of voluntary grasp did not occur in the older group. The younger animals began to vocalize soon after surgery, while the older ones were practically "aphasic." The young animals also had earlier recovery of muscle tone than the older animals.

In electroencephalographic recordings of the monkeys, no electrical activity was noted on the side of operation, yet activity remained normal in the records made from the intact brain hemisphere. Results of the study were reported at the Seventh International Neurological Congress, Rome, Italy.

Maturational changes in brain wave patterns of normal monkeys studied

Studies of normal rhesus monkeys at NINDB's Laboratory of Perinatal Physiology, Puerto Rico, have added to knowledge of changes in the brain's electrical activity that occur during growth and maturation. In general, patterns of electrical activity (electroencephalograms) in the monkeys followed developmental trends found in other animals and man; that is, the greatest changes occurred shortly after birth but soon became stabilized into the adult forms.

During the first month of life, the EEG patterns remained similar to those found on the first day of life, but in the second month a marked change in amplitude and rhythm occurred. At 1 year of age, an adult pattern was seen which continued throughout the 30-month period of observation. Results also showed the differences between wakefulness and sleep patterns could be discerned on the first day of life, i.e., earlier than previously thought.

In addition, maturational changes in sleep patterns occurred earlier and developed more quickly than those of the waking state. About the end of the first week of life, sharp waves or "spikes" bearing a considerable resemblance to epileptic patterns were observed in the drowsy state and are considered to be a normal occurrence.

The study was conducted by Dr. Maria I. Robert de Ramires de Arellano of the NINDB Laboratory of Perinatal Physiology and was reported in Experimental Neurology.

New syndrome due to compression of the vertebral arteries identified

A new disease entity in which rotation or extension of the neck may compress the vertebral artery and impair the blood supply to the brain stem has been described in living patients by Wayne State University scientists. The disease is associated with the presence of bony growths in the neck vertebrae (cervical spondylosis), and often occurs in patients with atherosclerosis or other blood vessel abnormalities. The new syndrome, which is now believed to be common, was verified clinically and by arteriography in 26 patients.

Previously, obscure neurological syndromes caused by cervical spondylosis were ascribed to direct compression of the spinal cord or nerve roots. Recent autopsy studies, however, verified that vertebral growths, which commonly occur in the neck, could cause displacement and compression of the vertebral artery when the neck was rotated.

To perform arteriograms, a simple and safe technique was developed in which the vertebral artery was visualized by catheterization and injection of an artery in the arm. Spondylotic compression of the vertebral arteries was confirmed in 26 of 48 patients, and arteriorgrams made before and after neck rotation showed that this maneuver often increased arterial compression. In addition, atherosclerosis or arteriosclerosis of the cerebral vessels was present in many patients, and probably predisposed the person to symptoms.

Clinically, the most common symptoms were found to be dizziness and vertigo, ataxia, visual disorders, headache, and paralysis. Several patients suffered from "drop attacks," a transient paralysis without loss of consciousness.

According to the findings, the new disorder occurs most commonly in the sixth decade of life, and is more common in males than females. Symptoms are episodic and are amenable to treatment in the early stages, although repeated attacks may produce progressive and irreversible damage to the brain stem. The study, jointly supported by NINDB and NHI, was conducted by Drs. Sheila Sheehan, Raymond Bauer (NINDB special clinical trainee), and John S. Meyer, Wayne State University College of Medicine, Detroit, and is reported in Neurology.

EEG changes correlated directly with release of antidiuretic hormone

A finding which will aid investigators in further defining the mechanisms for release of antidiuretic hormones has been reported by NINDB grantees. Electroencephalographic studies have shown that distinctive electrical signals from certain parts of the brain are temporally related to decreased flow of urine, and thus to the release of antidiuretic hormone (ADH). The demonstration of this relationship suggests that brain wave recordings can be used to localize sensory elements in the brain which are thought to influence hormone release.

Conducted by Drs. Charles H. Sawyer and George R. Fuller of the University of California School of Medicine, the study is representative of numerous attempts to elucidate the factors which govern the release of ADH. Previous work by Drs. E. B. Verney and P. A. Jewell showed that increases in blood osmotic pressure trigger the release of ADH by activating a type of sensory element, termed "osmoreceptors," found in several brain areas. Other recent studies have attempted to locate the sites of the "osmoreceptors" by correlating electrical activity with ADH release. The present study has confirmed such studies by demonstrating that a functional relationship exists between changes in electrical activity and osmoreceptor activity.

In performing their experiments, the investigators injected hypertonic saline into large brain arteries of the cat and rabbit to change osmotic pressures. Immediately, they observed characteristic electrical changes and a concomitant decrease in the flow of urine. The electrical changes appeared to originate from specific areas in the olfactory system of the brain. In general, these areas were similar to those previously suggested as sites of osmoreceptor activity. From these results, the authors theorize that the osmoreceptors may consist of specialized neurons which are especially sensitive to certain types of chemical changes in the blood. The study was reported in Electroencephalography and Clinical Neurophysiology.

Importance of metabolic pathway in brain development underscored by NINDB study

A striking parallel between a specific enzyme activity, and cell growth and development in the embryonic chick brain suggests that an alternate metabolic pathway is essential to the synthesis of proteins and other substances in the developing nerve cells of the brain.

Fluctuations in the activity of the enzyme, glucose-6-phosphate dehydrogenase, were measured in 54 chicken embryos at various stages of incubation. The changes in the activity of this enzyme are an indication of the activity of the pentose cycle of carbohydrate metabolism; this cycle, one of the three major pathways of carbohydrate metabolism, appears to be of great importance during the early development of the embryonic chick brain.

Experiments were based on the knowledge that the development of the central nervous system is characterized by a period of intense cell production followed by periods of greatly reduced activity during which new materials, principally proteins, are synthesized.

Comparison of the fluctuating activity of the enzyme with ribonucleic acid (RNA) concentration indicated that the maximum activity of the pentose cycle follows peak cell production, and is probably related to the cell development and differentiation which follows. Considering the importance of RNA to protein synthesis, the authors postulated that the increasing pentose cycle activity, just prior to differentiation, may result in a significant contribution of pentose for the synthesis of RNA.

Drs. Alvin M. Burt and Byron S. Wenger of the University of Kansas reported their results in Developmental Biology.

Care in use of urea to reduce brain-swelling cautioned

An NINDB-supported study has shown that the amount of urea to be used with low temperature surgery must be very small in order to avoid severe cardiac difficulties. Otherwise, under combined low temperature and urea treatment, changes in important blood constituents were enough to precipitate ventricular fibrillation, a serious irregularity of heart action.

Since concentrated urea reduces brain volume and lowered body temperature (hypothermia) permits reduced or arrested circulation for "bloodless" surgery, the concurrent use of the two techniques would appear to offer advantages. An investigation by Drs. Edgar A. Bering and Nurhan Avman of Harvard Medical School determined that although hypothermia in dogs caused a decrease in intracranial pressure, urea injections always caused an additionl decrease. Hypothermia prolonged the state of decreased pressure caused by the urea and there was a loss of important blood constituents—salts and electrolytes. The loss of these constituents, important in the control of cardiac function, was enough to initiate ventricular fibrillation.

In order to avoid these cardiac complications the investigators suggest that the amount of urea used with hypothermia can be reduced to about one third or fourth of the dose used at normal temperature. Because of the added effect of hypothermia, this amount of urea should be sufficient to achieve adequate cranial space for surgical procedures.

In addition, severe changes in blood constituents caused by a rapid injection of urea at normal temperature were found to cause marked changes in the electrocardiogram. These findings, reported in the Journal of Neurology, indicate the dangers inherent in a large, rapid injection of urea at any temperature.

CHRONIC NEUROLOGICAL DISORDERS OF INFANCY AND CHILDHOOD

Eye movements of newborn infants provide early clues to neurological disease

A preliminary evaluation of a neurological test for newborn infants indicates that all normal newborns should respond to rotation with involuntary rapid movements of the eyeball known as nystagmus. A total absence of this response appears to be a sign of grave abnormality of the nervous system. Since response to vestibular stimulation by rotation may vary considerably in infants, criteria for interpreting the results of this test have been suggested by investigators participating in NINDB's Collaborative Project.

Drs. Murray E. Pendleton and Richmond S. Paine, Harvard Medical School and Children's Hospital Medical Center, Boston, tested the eye movements of a series of normal and abnormal full-term newborn and premature infants. An electrically driven table was used to provide constant rates of rotation and deceleration. Photographic and electro-oculographic recordings were employed, as was direct observation.

The investigators concluded that rotational nystagmus should be present in all normal full-term and normal larger premature infants, provided the infant is thoroughly awake. However, a number of infants were found to exhibit only simple deviation of the eyes with no active nystagmus. This response could be correlated with the following conditions: sleepiness, prematurity, heavy maternal anesthesia, anoxia or traumatic birth, and marked jaundice. Since an alteration of the state of consciousness is common to all of these conditions, the absence of nystagmus appears to be an early and sensitive index to consciousness. In a few infants who exhibited other symptoms of abnormal central nervous system function, neither response could be obtained.

These results confirm that the test for rotational nystagmus is a valuable part of the clinical neurological examination of newborn infants. If abnormal, it is an important clue to depressed nervous system function and an addition to the limited number of criteria available at this age.

Simple test may help wipe out one form of mental retardation

A new kind of test, based on a bacterial inhibition principle, may help wipe out one form of mental retardation. This test, which detects the disease known as phenylketonuria or PKU, was developed by Dr. Robert Guthrie, NINDB grantee at the University of Buffalo. PKU is an inherited condition which damages the brain by storing excessive amounts of phenylalanine in the blood. Early detection is essential, since persistence of high blood levels of phenylalanine rapidly leads to irreparable damage. A special phenylalanine-free diet can prevent this complication.

The new test is simple, inexpensive and uses but a drop of blood. It is based on a different principle than a previous test, also using but a drop of blood, developed by Dr. Bert La Du of the National Institute of Arthritis and Metabolic Diseases. Dr. La Du's test is designed to very accurately measure low levels of phenylalanine in the blood whereas Dr. Guthrie's test is more applicable to mass screening procedures.

Using this new procedure a technician can complete over 300 tests a day. A drop of blood from the baby's finger is blotted on a filter paper which is mailed to a laboratory, where a special analysis detects the one baby in 20,000 that has PKU. Detection is based on the fact that phenylalanine promotes the growth of a specific bacteria under certain conditions.

Other older blood tests required complicated analysis, and were less sensitive. Urine analysis, though simple, failed to produce a positive result until several months after birth, even though the phenylalanine in the blood increased to dangerous levels during the first few days after birth. Also, many PKU cases were missed by this test when phenylalanine levels were low but damaging.

Dr. Guthrie described this new test at the annual convention of the National Association of Retarded Children.

Cigarette smoking associated with premature birth in cooperative NINDB study

A significant correlation between cigarette smoking and incidence of premature birth has been demonstrated in the first prospective study of smoking and prematurity, conducted by NINDB with the Baltimore City Health Department. In this study, birth weight was taken as the index of prematurity—children weighing 5½ pounds or less being so considered. Premature infants were born to 18.4 percent of mothers in the study who smoked cigarettes, compared to 11.2 percent of nonsmoking mothers. In addition, the rate of premature birth was found to increase in proportion to the amount smoked.

The NINDB-supported study, which corroborates the results of previous retrospective studies conducted in California and in Birmingham, England, was conducted by T. M. Frazier and Dr. G. H. Davis of the Baltimore City Health Department and Dr. Hyman Goldstein and I. D. Goldberg, Biometrics Branch, NINDB. Cigarette smoking histories were obtained from interviews with 2,736 Negro women seen at Baltimore Health Department prenatal clinics and delivered of single live infants at Baltimore City Hospitals. Data from the prenatal clinics and birth and death certificates were used to collect additional information.

Although the mean duration of pregnancy was similar in both the smoking and nonsmoking groups, the investigators found that infants of smoking mothers have a smaller average birth weight regardless of gestation (after 32 weeks). This finding suggests the involvement of a fetal development mechanism, rather than simply the premature onset of labor. Moreover, fetal and neonatal death rates were found to be higher for infants of cigarette smokers.

The study also showed an association between "nervousness" (as measured by a psychosomatic complaint score) and prematurity. The highest prematurity rate (23.0 percent) was found among the "nervous" smokers, compared with 16.9 percent for "normal" smokers. However, the rate for "nervous" nonsmokers (10.4 percent) was essentially the same as that for "normal" nonsmokers (11.3 percent).

Additional correlations showed that the difference in prematurity rate between the groups was independent of maternal age, blood group type, initial hemoglobin level, sex of child, work history, and education, as well as psychosomatic complaint scored. However, other factors not included in this survey remain to be considered. The authors conclude, "Until the role of smoking and its association with increased prematurity is determined, each obstetrician must decide whether or not to advise his patients to limit smoking."

The study was reported in the American Journal of Obstetrics and Gynecology.

High bilirubin levels in blood of "healthy" premature babies found unrelated to neurological deficits

A finding which questions the necessity of routine exchange transfusions to prevent brain damage in newborn premature infants with high serum bilirubin levels has been reported by NINDB grantees at Columbia University. A preliminary study showed no relationship between levels of serum bilirubin, a bile pigment, in premature newborns and neurological deficits at three years of age, when other predisposing factors were absent.

Although further evidence is necessary to support this hypothesis, Drs. Jack G. Shiller and William A. Silverman suggest that premature infants may be able to tolerate moderately high concentrations of bilirubin in the blood unless complicating factors known to precipitate brain damage are present. Such complicating factors are hemolytic anemia due to blood incompatability (erythroblastosis fetalis), excessive doses of vitamin K, or administration of sulfasoxazole. However, the magnitude of the risk of "uncomplicated" hyperbilirubinemia is not yet established.

The study included 110 premature infants who were examined in the neonatal period and again at three years of age. Although about one-fourth of the newborns had "uncomplicated" hyperbilirubinemia (maximal concentrations between 18 and 22 mg. of bilirubin per 100 ml. serum), no association could be found between the levels of bilirubin and subsequent neurological defects or mental retardation. Children diagnosed as brain damaged or retarded were found to have had varying degrees of bilirubinemia in the neonatal period. Moreover, none of the children exhibited the neurological signs usually attributed to kernicterus residua, a disorder where bile pigments affect the tissues of the brain. The study appeared in the American Journal of Diseases of Children.

Newborn baby reflex function elucidated by NINDB grantee

In a study of the characteristics of the grasping response in newborns, a striking interaction was found between the infant's head position and the ease of elicitation of the foot grasp response. Characteristics of the grasping responses were also defined, and optimum methods for eliciting these reflexes were determined. These findings, while adding to the knowledge of nervous system function in early life, also aid participtants in the Collaborative Project in more fully understanding the reflex tests and responses.

Two hundred "normal" babies, aged from 2 hours to 1 week, were tested to determine the characteristics of the palmar (hand) and plantar (foot) grasp responses, as well as to study possible relationships between these and the tonic neck response. The presence of the tonic neck reflex was found to enhance the grasp reflex in the foot on one side and inhibit the reflex in the foot on the opposite side. However, no similar relationship to the hand grasp response could be demonstrated.

Grasping responses in newborns were also compared with reflexes seen in older patients with brain damage. Characteristics of the responses were found to be different in such adults, where they occur on a background of a mature, but damaged, nervous system.

These studies by Dr. Seymour L. Pollack, Charity Hospital, New Orleans, were reported in the Archives of Neurology. Similar studies in older infants, premature infants, and brain damaged infants are being made by the author.

NEUROMUSCULAR DISORDERS

Cholinesterase activity localized in cultured skeletal muscle cells

Studies of living muscle cells grown in tissue culture without nerve tissue show that cholinesterase, an enzyme important in neuromuscular transmission, initially is located throughout the cell, rather than at the end-plate region of the nerve-muscle junction as in innervated muscle cells. No cholinesterate-containing end-plates were found in the cultured cells, but in the more mature stages the enzyme was located along certain cross-striated bands (Z-lines) which traverse the muscle fibers.

Cholinesterase is the enzyme which regulates neuromuscular transmission by destroying acetylcholine, a chemical necessary for the conduction of impulses across synapses and across the nerve-muscle junction. The localization of cholinsterase activity in skeletal muscle cells may lead to a better understanding of the mechanisms responsible for impulse transmission from nerve to muscle and, possibly, from the end-plate region to other parts of the muscle fiber. Sites of activity of the enzyme have been determined in living cells of chick embryo skeletal muscle by Dr. W. K. Engel, Medical Neurology Branch, NINDB and results published in the Journal of Histochemistry and Cytochemistry.

Since there is no direct method for the cytochemical localization of a specific cholinesterase, the enzyme was detected by its action on substrates introduced into the cells and by its susceptibility to various inhibitors. Under these circumstances, the enzyme demonstrated had properties like the specific cholinesterase known to be of physiological importance in muscle activity.

Cultured muscle cells in three stages of development showed sites of cholinesterase activity as small brown granules located diffusely in the cytoplasm and clustered in the regions around the cell nuclei. However, no enzyme activity was found in the cell membrane surrounding the muscle fiber or within the nuclei. The finding that no motor end-plates were formed by the muscle cells suggests that nerve tissue is essential for the development of end-plate structures. It also appears that before innervation cholinesterase activity is widely distributed throughout the cell. Subsequent to innervation, enzyme activity is increased at the motor end-plates and repressed elsewhere.

The demonstration of cholinesterase along the transverse striations known as Z-lines raises an additional consideration: that is, whether or not a mechanism involving cholinesterase and acetylcholine may be active along the Z-lines to conduct the activating impulse into the center of the skeletal muscle cell and thus activate the muscle fiber. Previous physiological studies by other investigators indicate that incompletely innervated muscle cells and denervated adult muscle show, in regard to sensitivity to applied acetylcholine, a similar diffuse pattern along the muscle fibers. Thus, support is added to the suggestion that under certain conditions an acetylcholine-cholinesterase mechanism may function at sites of the muscle fiber other than the motor end-plate.

Rare muscle cell abnormality investigated by NINDB scientist

A rare disease of muscle characterized by a weakness in the hips and shoulders was investigated by the collaboration of an NINDB investigator with a group of scientists at the National Hospital and the Institute of Neurology, at University College, and at Guy's Hospital in London, England. The patient with this disease always has had specific difficulty in rising from a chair, climbing stairs and lifting objects above shoulder level.

Dr. W. K. Engel, NINDB, collaborated with Drs. J. B. Foster, B. P. Hughes, H. E. Huxley, and R. Mahler in an extensive study of a 19-year-old male with this disorder, called central core disease.

Histochemical and electron microscopic examination and biochemical study of muscle biopsy tissue samples revealed an abnormal core of material in the muscle cells of the patient and a biochemical abnormality in both the patient and his otherwise normal father. The study of the patient's family indicated a possibility of the father being a carrier of the disease without being clinically affected himself.

The authors propose that the disease is congenital and that it probably affects the normal development of muscle fibers. Since the probable carrier of the trait may show no clinical or histological evidence of the disease, more than one genetic factor must be responsible for the full manifestation of the disease. They suggest a variety of possibilities for the development of the central core in the muscle cells.

The results of this study were reported in Brain.

AMYOTROPHIC LATERAL SCLEROSIS AND PARKINSONISM-DEMENTIA COMPLEX

Study in Guam suggests relationship between amyotrophic lateral sclerosis and Parkinsonism-Dementia Complex

Scientific investigation of the indigenous Chamorro population of Guam suggests that amyotrophic lateral sclerosis and a recently described disorder Parkinsonism-Dementia Complex, may be clinical variations of the same disease. Although factors responsible for the spectrum of clinical manifestations are as yet unknown, a genetic basis for the two disorders has been suggested.

The close relationship between the two disorders among the Chamorros is suggested by the similarities of the age, sex, and geographic distribution of the cases, by the duration from onset to death, by the histories of the occurrence of one or both disorders in siblings and other relatives, and by the pathological and clinical features common to both disorders.

This study was carried out by Drs. Asao Hirano, Visiting Scientist, NINDB, Leonard T. Kurland, Chief of Epidemiology Branch, NINDB, Nathan Malamud, University of California, and S. Lessell of the NINDB Research Center on Guam.

Parkinsonism-Dementia Complex has been endemic in Guam for several decades, affecting one in 200 with a death ratio of about 7 percent among adults. Amyotrophic lateral sclerosis accounts for about 10 percent of adult deaths—100 times the ratio reported in the continental United States.

The principal clinical features of Parkinsonism-Dementia Complex are progressive mental deterioration, hyperreflexia, and loss of automatic movements (akinesia). Staring, tremor, rigidity, and other Parkinsonian features may also be present. The mean age at onset for Parkinsonism-Dementia Complex is 50 years and it affects about three men to every one woman. Death usually occurs within 3 to 5 years.

If an external factor cannot be detected, the conclusive establishment of a genetic mechanism for the syndrome will depend upon the identification of some biochemical abnormality, detectable prior to its onset.

This study was reported at the American Neurological Association meeting.

EPILEPSY

Epilepsy in experimental animals arrested by anticonvulsant drug

Previous studies have revealed that in epilepsy due to damage or lesions in localized areas of the brain there is a tendency for the gradual development of secondary lesions that add to the severity of the disease. While early surgical removal of a primary lesion may prevent the development of secondary lesions, most patients are treated medicinally rather than surgically. The NINDB grantees considered it highly pertinent to determine whether long-term administration of an anticonvulsant drug could also prevent the establishment of independent secondary lesions.

They studied the effect of two anticonvulsant agents and a tranquilizer on 30 guinea pigs with experimentally induced lesions. Electroencephalograms of these animals were analyzed for indications of epileptic discharge in the brain.

The anticonvulsant, phenobarbital, commonly used to treat the symptoms of epilepsy, has been shown to arrest further development of the basic disease in experimental animals. Another anticonvulsant, diphenylhydantoin, also effective in controlling the symptoms of epilepsy, did not retard the development of the disease.

Of the three drugs tested, only phenobarbital was found to retard the establishment of secondary lesions in the guinea pigs. Noting the hazards in drawing conclusions from animal experiments to human disease, the investigators warned that these findings question the advisability of long-term treatment solely with diphenylhydantoin in patients with discrete and accessible lesions.

Dr. Frank Morrell and Mr. Lowell Baker, University of Minnesota Medical School, reported their findings in Neurology.

HEADACHE

Brain wave patterns reflect cause of some vascular headaches of migraine type

The incidence of abnormal brain wave patterns in patients suffering from vascular headaches of the migraine type has been found to be about twice that found in normal subjects in a study conducted by Drs. Walter A. Camp and Harold G. Wolff, NINDB grantees at New York Hospital and Cornell University Medical College. Consequently, the investigators have correlated some types of brain wave abnormalities occurring in these patients with the pathological factors likely to cause them.

In a group of patients with vascular headaches of the migraine type, brain wave abnormalities (as recorded by electroencephalograph) were separated into two broad categories—those originating from a single area of the brain (focal) and persistent, diffuse disturbances (nonfocal). Analysis of the focal abnormalities suggests that they provide important clues to the mechanisms underlying brain dysfunction in these patients. The origin of the nonfocal abnormalities is not yet known.

On the basis of their findings, as well as of numerous studies reported by other investigators, Drs. Camp and Wolff propose that the focal electroencephalographic (EEG) abnormalities may be classified into three groups. In the first, EEG alterations and focal motor or sensory defects occur briefly during a headache; the cause of this type is probably circulation impairment due to vasoconstriction. In the second, EEG abnormalities and neurological defects may persist for hours or days after the headache, and the suggested pathological process is local brain edema, or fluid accumulation. (Such edema may be due to prolonged circulation impairment or, as the authors postulate, to a separate neurogenic factor linked with dilation of the blood vessels.) A third group consists of persistently abnormal EEG recordings during a headache-free period, which occur in patients with conspicuous motor, mental or sensory abnormalities during the migraine attack. This type is probably precipitated by cerebral infarction.

A detailed description of this study appears in the Archives of Neurology.

PAIN

Permanent electrodes in thalamus of the brain used to relieve chronic pain

One approach to the problem of treating chronic severe pain is being evaluated by NINDB grantees who report that permanently implanted electrodes in the thalamus of the brain provided some relief of head and neck pain in patients with terminal cancer of the head and neck. The use of permanent electrodes enable the investigators to enlarge thalamic lesions when pain recurred, without causing debilitating sensory losses or personality changes.

This study is representative of numerous research efforts to develop more effective and acceptable procedures for controlling extreme pain. Other promising research approaches include studies of the activity and effects of many pain-relieving drugs or agents, evaluations of various surgical techniques for interrupting pain pathways, and related basic studies of nerve structure and function.

In the current study, stereotactic thalamotomy provided some subjective relief of head and neck pain in 13 of 14 patients. Some experienced complete relief with little or no sensory loss, suggesting that areas of the thalamus other than the sensory relay nucleus had been destroyed. On the other hand, two of three patients with upper extremity pain were not benefited, in spite of a striking sensory loss. The latter finding implies that more than one nerve pathway exists for the transmission of a given sensation, since perception of subjective pain sensations seemed unrelated to perception of such other sensations as pin pricks or temperature changes.

Electrodes implanted for periods varying up to 9 months afforded a period of pain relief consistent with the life-expectancy range of the patients. In addition, the technique allowed the investigators to check the accuracy of stereotactic methods for electrode placement, as well as to observe aspects of thalamic function in unanesthetized patients. The study was reported by Drs. Vernon H. Mark, Frank R. Ervin, and Thomas P. Hackett, Massachusetts General Hospital and Harvard Medical School, Boston, in Archives of Neurology.

DISORDERS OF VISION

Studies suggest that inhibitory nerve fibers help to regulate visual function

Recent NINDB studies indicate that inhibitory, as well as excitatory, nerve fibers lead from the thalamus to the visual center of the brain's cerebral cortex. Recordings of the electrical activity of single brain cells, after thalamic stimulation, showed evidence of both excitatory and inhibitory activity. These results suggest that the process of inhibition may play an important role in regulating visual function.

In order to study brain cell activity, electrical stimulation was applied to the lateral geniculate body, a thalamic center which receives impulses from the eye and relays them to the brain. The response of cells in the visual cortex was simultaneously recorded by intracellular electrodes and by electrodes on the brain's surface.

The experiments demonstrated that hyperpolarization was an outstanding feature of the responses recorded from neurones in the visual cortex. Hyperpolarization potentials are found when a cell's electrical activity is suppressed or inhibited; depolarization is accompanied by the repetitive firing of an excited cell.

Immediately after stimulation of the lateral geniculate body, many cortical cells showed an initial excitation and depolarization, followed by inhibition and hyperpolarization. Therefore, the stimulus may have activated both excitatory and inhibitory impulses, but the excitatory impulses arrived at the cell more quickly. In some cases, initial excitation was obscured by an inhibition, and the response consisted of a small depolarization potential followed by hyperpolarization. Other neurones exhibited only hyperpolarization.

Previous studies by other investigators have indicated that inhibitory processes may also affect the activity of spinal motor neurones and the stretch receptor cells. In addition, inhibitory areas have been demonstrated in the cat retina. The present investigations were conducted by Drs. Choh-Luh Li, Armando Ortiz-Galvin, Shelley N. Chou, and Saxton Y. Howard (deceased) of the Surgical Neurology Branch, NINDB. The results were reported in the Journal of Neurophysiology.

Study suggests that hyaluronic acid acts as a diffusion barrier in the eye

Hyaluronic acid, a mucopolysaccaride found in the ground substance of various tissues, was first isolated from the vitreous body of the eye. Recent *in vitro* studies on the filter action of this substance by NINDB grantees support the theory that hyaluronic acid acts as a "molecular sieve" which allows the passage of small particles, but holds back particulate matter of larger diameters. Clarification of the role of hyaluronic acid as a diffusion barrier in the vitreous body is of particular importance since the problem of the persistence or resolution of vitreous opacities which interfere with vision might be related to the physical states of the mucopolysaccharide.

The diffusional movement through hyaluronic acid solution of such materials as lens protein, albumin, fibrinogen, and polystyrene latex particles was studied by Drs. T. C. Laurent and A. Pietrusziewicz, of the Retina Foundation, Massachusetts Eye and Ear Infirmary, Boston. Using the ultracentrifuge, the investigators measured and compared the diffusion rates and the sedimentation rates of particles in hyaluronic acid of varying concentrations.

In the presence of higher concentrations of hyaluronic acid, the sedimentation rates of the larger particles decreased up to 5,000 times, suggesting that the particles were being held suspended in the solution. Under the same conditions, the rate of sedimentation of the smaller sized materials decreased only about 25 percent. The diffusion rate and the sedimentation rate were found to be the same phenomenon, since the ratios between them were always the same in the various concentrations of the acid.

Analysis of these results showed linear relationship between the decrease in sedimentation rate and the concentration of hyaluronic acid. In addition, the sedimentation rate was related linearly to the molecular size of the particles. Between these two linear relationships, the authors found a direct relationship. This evidence indicates that two factors regulate the movements of particles in hyaluronic acid—that is, the size of the particles and the acid concentration.

A model experiment was then devised to demonstrate how molecules of hyaluronic acid might entangle and form a three dimensional network to filter out large particles. Mathematical calculations demonstrated a relationship very similar to that found in the preceding experiments.

In the vitreous body of the eye, the concentration of hyaluronic acid is known to be highest at the periphery and low in the central part. Employing the above results, the authors calculated the probable mobility of the different materials throughout the vitreous body. Large particles such as viruses or cells, they speculate, are held back effectively at the surface layer of the body, whereas small sized particles might enter freely from the vitreous into neighboring tissues and fluids.

The study was reported at the Eastern Section Meeting of the Association for Research in Ophthalmology held at NIH.

Relationships between vitamin A availability and retinal function clarified

Comprehensive studies by an NINDB grantee at Harvard University have demonstrated in detail the complex relationships between the availability of vitamin A and retinal function. One important result was to show that the electrical sensitivity of the eye parallels the rhodopsin (visual purple) concentration in both normal and vitamin A deficient rats. This correlates well with the psychophysical changes and rhodopsin concentration of human eyes during dark adaptation.

By maintaining young rats on a vitamin A deficient diet which produced selective damage of the retina's visual cells, Dr. John E. Dowling was able to observe the process of retinal degeneration more slowly than ever before. He was able to keep the advanced vitamin A deficient rats alive by supplementing their diet with vitamin A acid, which supplies the somatic needs of the body in general for vitamin A but not those of the retina.

Such animals develop progressive night blindness, and the outer segments of the retinal layer containing the visual cells slowly degenerate. The pattern of degeneration was similar to that described for several hereditary conditions resulting in night blindness in man and animals, such as retinitis pigmentosa. Several months later, the rest of the visual cells were seen to degenerate, causing total blindness.

When vitamin A was supplemented to animals with severe night blindness, however, visual recovery occurred if the retinal degeneration had not progressed too far. Histological studies provided the first conclusive evidence that the outer segments of partially damaged rod cells are capable of spontaneous recovery, where the basal portion of the cell was intact. With further development, this finding has significant implications for both clinical and basic ophthalmology. The studies were reported in the American Journal of Ophthalmology.

Frozen material used for successful corneal grafts

For many years doctors have cured blindness caused by scarring of the cornea by grafting on a new piece of cornea from an eye which had been removed just a few hours after the donor's death. Recently methods have been devised to preserve the corneas by dehydration or deep freezing. The advantages of long-term storage and easy transport are obvious.

Previous investigators had reported favorable results when using tissue which had been dehydrated. The present investigators tested the merits of donor material stored in the deep-frozen state without dehydration. They indicated that simple freezing over solidified carbon dioxide (dry ice) is rather simple and may therefore have some practical advantages over dehydrated tissues.

No significant difference could be detected between 28 corneal grafts using frozen material and 27 operations using fresh donor material; although during healing there was possibly more edema and vascularization in the cases where frozen material was used.

The study was conducted by Drs. E. C. Sweebe and C. H. Dohlman, NINDB grantees at the Massachusetts Eye and Ear Infirmary and the Retina Foundation, Boston, and reported in the Archives of Ophthalmology.

Simple test used to assess visual field defects

Color plates, originally designed to detect congenital color deficiencies, have been shown to have apparent clinical value in diagnosing visual field losses in patients with varying degrees of brain damage. Consistent patterns of visual defects were obtained from some otherwise uncooperative patients with severe mental changes who could not be tested by conventional methods. These tests, which may be rapidly administered at the bedside, and may be easily repeated, have occasionally demonstrated visual deficits not found by standard perimetry.

Seventy-five patients, in a study aided in part by a NINDB grant, were tested with color plates and with standard field measurement techniques. There were

32 cases of partial blindness in one or both eyes, 9 cases of bitemporal defects, and 34 cases with normal visual fields.

Many of the patients had difficulty identifying numbers on the color plates or consistently reported only one of the two-digit numbers even though the cards were presented to a portion of their visual field which was seemingly normal as determined by standard methods of visual field measurement. Deficiencies in color perception, ability to perceive two targets simultaneously exposed, and discrimination of dotted figures in dotted field were also noted in the tests.

The investigators suggest that the conventional field measurement techniques are limited and reveal only certain aspects of visual field deficit after brain damage. However, other factors shown to influence the results of conventional testing methods must still be evaluated with respect to the use of color plates.

The study by Drs. Stanley M. Silverman, Philip S. Bergman, Morris Bender, and William Battersby, Mount Sinai Hospital, New York, was reported in Archives of Neurology.

Wound-healing process studied in mast cells of cornea

Specific cells which surround the cornea appear to prevent the formation of blood vessels in the cornea, except in the presence of a wound which destroys these cells (called mast cells). When injury involves the mast cells, the barrier is broken and blood vessels form, making the healing process more analogous to that in other parts of the body, and often leading to permanent opacities of the cornea.

The study was reported in the Archives of Ophthalmology by Dr. Richard S. Smith, NINDB grantee, in the Department of Ophthalmology Research, College of Physicians and Surgeons, Columbia University.

Dr. Smith, after anesthetizing the eyes of 16 rats, produced injury to the entire surface of the cornea. Seven days later he observed blood vessel forming over the surface of the cornea, extending inward. After 16 days blood vessels covered the entire cornea, and, for the first time, mast cells were visible. The investigator had noted that in the normal eye there was an abundance of mast cells outlining the junction between the sclera and the cornea (limbus). On the 16th day, this concentration was no longer present, but during the next 2 weeks mast cells gradually invaded the cornea, extending finally to the center.

The purpose of Dr. Smith's work was to confirm the presence of mast cells in the injured cornea and to study the details and possible implications of their formation, in an effort to learn more about the origin and physiological function of these connective tissue cells, whose role in wound healing has been in doubt.

Dr. Smith knew that if injury to the cornea is far enough away from the limbus it heals without the presence of blood vessels or mast cells. If the trauma is within a certain critical distance of this limbus, blood vessels appear in that part of the cornea as part of the healing process. Once the blood vessels are present, mast cells also appear.

He concluded that the mast cells at the junction of the sclera and cornea inhibit corneal vascularization in some way and that when massive injury to the cornea destroys them, there is a physical or biochemical change in the stability of the system, with subsequent vascularization.

DISORDERS OF HEARING

NINDB grantees establish tenative norms for hearing ability at advanced ages

The results of a recent study have provided tentative norms for minimum levels of hearing and for the ability to distinguish various sounds at advanced ages. The relationships between the tests used in this study indicates that hearing problems of the aged are probably due to a composite of factors rather than caused by degenerative changes at any particular level of the auditory system.

Noting the lack of norms for tests of hearing ability for the increasing number of people over 65 years of age, NINDB grantees tested 45 men and women between the ages of 60 and 90 years. Selection criteria were designed to exclude subjects who had hearing losses due to causes other than old age. After a battery of tests measuring minimum levels of hearing for pure tones and speech, ability to distinguish spoken words, and apparent changes in pitch of a constant tone were given, the effects of age and sex on the tests were analyzed and the relationships among the several tests were determined. For the subjects tested, all tests, except the one for detecting apparent changes in pitch of a constant tone, indicated a decreasing hearing ability with increasing age and showed neither sex differences nor differences in right or left ear.

Clinical observations have established that older people have poorer discrimination abilities than people below 40 years of age even though they both may have similar pure tone sensitivities. Also, any one discrimination test may show little correlation with age. Therefore, the authors suggest that the difference between the results of an easy and difficult discrimination test would be a more meaningful measure of general auditory ability. The difference scores in this study increased with increasing age of the subjects.

Although discrimination problems of the aged have been associated with degeneration of neurons in the brain, the correlation studies between the tests and chronological age indicated that the difficulties are the result of a composite of factors involving all levels of the hearing mechanism.

This study, by Drs. C. P. Goetzinger, G. O. Proud, and James Embrey and Mr. Donald Dirks, Kansas University Medical Center, appeared in Archives of Otolaryngology.

Serum project may provide clues to neurological disorders in infants

Blood samples from more than 75,000 expectant mothers may provide the answer to the role virus infection plays in mental retardation, Mongolism, cerebral palsy, and other neurological disorders with which infants sometimes are born. In an unprecedented study, serum from these blood samples is being tested by NINDB scientists as part of the Institute's Collaborative Project.

The serum phase of the Project makes use of antigens—substances which stimulate a chemical defense mechanism in the blood—to test the patient's serum for evidence of having been exposed to certain viruses. If a patient has been exposed to infections, this will be indicated by a greater number of antibodies in her serum.

At each of the 15 collaborating medical centers, blood samples are obtained from the patients during pregnancy and are sent to NINDB at Bethesda, Md., for testing. The serum is stored at minus 10° F. in two huge, walk-in freezers—1,390 square feet in total size—in the Section on Virology known as the Serum Center. Here, specific information concerning the patient's pregnancy is kept along with data concerning the sample of serum, which is readily available for checking and rechecking for many years.

To test the serum, the Section on Virology produced an extensive panel of more than 100 viral antigens. Among these are 3 polio viruses, 28 ECHO viruses, 30 Coxsackie viruses, 28 Adeno viruses, and 9 Myxo viruses. These range from common cold viruses to those that cause paralysis and death.

Development of the antigens has required extensive work in bringing together specific viral materials, performing many complicated tests, developing new tests, and in many instances developing suitable conditions to grow the virus for antigen production.

Five key developments cited in perinatal research project

By January 1, 1962, the Collaborative Perinatal Research Project will have been in operation for 3 years. The primary goal of the Project is to discover clues to the prenatal causes of cerebral palsy, mental retardation, and other neurological and sensory disorders of infancy and childhood. To this end, 15 hospital teams of medical and allied scientists will eventually study some 50,000 expectant mothers from early pregnancy through labor and delivery, and will examine their children periodically from birth through school age.

The Project's third year was marked by five key developments. First, an obstetric diagnostic summary sheet was designed to simplify linking disorders in pregnant women with disorders in their children. Second, a speech and hearing examination for 3-year-olds and a psychological examination for 4-year-olds were developed to aid in the identification of children with brain damage. Third, a gross autopsy procedure and form were designed which will enable pathologists to collect important post-morten information on Project children who are born dead or die after birth. Fourth, plans were begun for a statistical analysis of prematurity, which is an important factor in infant deaths as well as in brain damage in children. And fifth, the number of women and children enrolled in the Project continued to mount: by the end of September 1961, the 15 colaborating institutions had sent the Institute records on about 20,000 mothers and 15,000 children.

Workshop on a "Definition of Blindness" organized

A group of some 21 people, consisting of professional workers among the blind, social workers, statisticians, Bureau of State Services representatives and NINDB personnel, have formed a Workshop on a "Definition of Blindness."

An active subcommittee is working on low vision vocational rehabilitation services. They are developing a simplified examination form for the use of ophthalmologists. They plan to make it available to a group of selected centers first for pretesting.

A "behavioral" subcommittee is developing a questionnaire to be submitted to all voluntary and governmental agencies in an effort to find out what types of visually handicapped persons they are interested in rehabilitating and how their services are administered.

Program project grants awarded

In August 1960, in taking action on the fiscal year 1961, Labor, Health, Education, and Welfare appropriations, the Congress extended to NINDB, and five other Institutes, authority for the establishment of centers for clinical research. Congress also appropriated $500,000 to NINDB for categorical clinical research centers.

Under this new authority and with Congressional emphasis on broad programs, the NINDB Advisory Council recommended approval of five "Broad Program Project Grants." These included research programs at Cornell University Medical College, State University of Iowa, Albert Einstein College of Medicine, University of Wisconsin, and Yeshiva University.

The emphasis of these programs is on cerebrovascular disease, neuro-sensory disorders, clinical neurology, epilepsy, and brain damage and defective brain development in children.

Cooperative glaucoma detection study continues

The 5-year cooperative study with the Bureau of State Services, now in its second year, continues the evaluation of techniques for detecting and identifying glaucoma. A protocol and standardization for testing has now been developed and will be made available to ophthalmologists for practical tests.

Methods presently applied for screening and diagnosing glaucoma are being evaluated at the Wilmer Institute, John Hopkins University Hospital, Baltimore; the Moffitt Eye Hospital, University of California Medical School, San Francisco; the Department of Ophthalmology, State University of Iowa, Iowa City; and the Department of Ophthalmology, Washington University School of Medicine, St. Louis, Mo.

Research projects supported abroad

Laboratories outside the borders of the United States frequently have a unique potential for contributing to research into neurological and sensory disorders. During the past year, NINDB supported 63 research projects abroad, representing 5 percent of the total number of projects supported. Funds for support of these international projects totaled one million dollars, with research grant support occurring in 22 countries from Australia to Iceland.

During 1961, plans were formulated for establishing an international biomedical research program. This envisages some form of collaboration between American institutions and institutions outside the United States. The program is for the specific purpose of utilizing the combined efforts in attacking a problem or in evolving a facility to the benefit of neurology in general.

More than 1,500 delegates from 48 countries attended the Seventh International Congress of Neurology which met in Rome, Italy, in September of 1961. A feature of the Congress was a large number of symposia on various neurological disorders, including aphasia, multiple sclerosis, muscular dystrophy, epilepsy, and Parkinson's disease. A grant from NINDB made possible the simultaneous translation of the proceedings in English, French, German, and Italian.

In addition, NINDB continues to support certain research planning activities of the World Federation of Neurology, an international professional organization with headquarters in Antwerp, Belgium. Through a grant from the Institute, the Federation is undertaking to develop a methodology for an international cerebrovascular study of the epidemiology and neuropathology of stroke. Factors which cause stroke in different national, ethnic, racial, and cultural groups throughout the world are to be investigated.

CONFERENCES

NINDB-supported conference focuses attention on problems of cerebral dominance

In a multidisciplinary approach to the unsolved problems of brain structure and function, international authorities pooled their ideas and findings at a recent conference on cerebral dominance. Dr. John E. Bordley, Johns Hopkins, was chairman of the 2-day conference, which was jointly supported by NINDB and the John Hopkins University School of Medicine.

A discussion of the possible existence of anatomical asymmetries between the brain's hemispheres was the subject of the first half-day session. Athough this concept would account for physiological observations, the group concurred that few gross anatomical asymmetries could be demonstrated. The second major topic concerned mechanisms for functional integration between the hemispheres of lower animals. Studies were presented which elaborated on the pioneering work in this field of Dr. Roger W. Sperry of the California Institute of Technology, who was chairman of the discussion.

In a third session, the functional differences between the hemispheres of the human brain were discussed from the viewpoint of psychology. The problem of defining the concept of dominance was also introduced. Functional differences were further clarified by clinical neurologists in a final discussion.

Among the scientists who participated in the conference were Drs. Macdonald Critchley and George Ettlinger, National Hospital, Queen Square, London; Dr. Richard Jung, University of Freiburg, Germany; Dr. H. Hecaen, St. Ann Hospital, Paris; Dr. Hans-Lukas Teuber, New York University College of Medicine; Dr. James O'Leary, Washington University; and Dr. Harold Wolff, New York Hospital.

World leaders in neuropathology speak at teaching symposium for young scientists

Many of the Nation's leading authorities in neuropathology and related fields served as a faculty at a unique teaching symposium at the University of Vermont, June 25. In an effort to stimulate young investigators to pursue research careers in neuropathology, current research and the challenge of unsolved problems were highlighted at the 4-day meeting. The symposium was arranged by the Pathology Study Section and supported by an NINDB grant.

By invitation, some 150 young investigators now training in neurology, pathology, and neurobiology attended the symposium. A program of formal lectures and informal discussions provided a comprehensive survey of the variety of research areas encompassed by neuropathology.

Although many presentations were concerned with molecular and cellular approaches to diseases and healthy nerve tissue, other reports involved the integrated nervous system. Several of these covered research in neuroembryology, concepts of mental disease, experimental demyelinating diseases, physiological aspects of certain manmade vascular diseases, neurotoxins, epidemiology in nervous diseases, and effects of radiation on the nervous system.

Among the many outstanding papers given were those of Drs. Sarah A. Luse, Eli Robins, and Rita Levi-Montalcini of the Washington University School of Medicine, St. Louis. Speakers from Israel and Great Britain participiated and a summation of the conference was made by Dr. Harry M. Zimmerman of Montefiore Hospital, New York. Chairman of the symposium was Dr. Samuel P. Hicks of Harvard Medical School and the New England Deaconess Hospital. Financial arrangements for the symposium were made through the latter institution.

NINDB supports conference on research potentials in voice physiology

Leading scientists from the United States and abroad reviewed the status of research on voice physiology at a 6-day conference at the State University of New York Upstate Medical Center, Syracuse. Findings resulting from research in a variety of disciplines were presented and a review of unsolved problems and possible areas of research in voice physiology was prepared by participating investigators.

At an initial session devoted to anatomy, Dr. Wolfgang Zenker, University of Vienna, reported the identification of specialized fibers in the vocal muscle. Significant findings were also presented and discussed at sessions on neurophysiology, physics, and electromyography. In discussions of high speed photography and stroboscopy, participants concluded that the stroboscope is an important clinical tool for the observation and treatment of laryngeal diseases.

Methods for producing "synthetic" speech and possible applications of the techniques were reported. Speech produced by electrical means without a specific human model may eventually permit the conversion of written material to speech. Further sessions dealt with voice diagnosis and therapy, relations with hearing and speech, pathology, and medical and surgical aspects of voice physiology.

PUBLICATIONS

New book evolves from drug therapy symposium

The proceedings of the Symposium on Evaluation of Drug Therapy in Neurological and Sensory Diseases are now in book form—entitled "Evaluation of Drug Therapy," published by the University of Wisconsin Press, and edited by Francis M. Forster.

The symposium from which this book evolved was held at the University of Wisconsin last year under the auspieces of the U.S. Public Health Service through the National Institute of Neurological Diseases and Blindness. Its aim was to determine the guidelines necessary for arriving at an ideal study for evaluating drug therapy under the criteria of the various panels.

At the symposium, panel groups in eight specific disorders reviewed the broad aspects of therapy and proposed methods for the most effective evaluation of drugs in each disease area. Sessions were held to discuss epilepsy, glaucoma, multiple sclerosis, vertigo, Parkinsonism, headaches, muscle diseases, and neuropathies and neuralgias.

The final section of this book consists of the eight panel reports composed of broad definitions of these areas of neurological diseases, lists of criteria for improvement of evaluation, and discussion of techniques and methodology for determining and testing results.

As a result of the symposium, individual groups are now actively concerned with headache, multiple sclerosis, epilepsy, and diseases of the muscle. Chairmen of these groups are developing classifications, methods of collecting data, and other aspects of their programs. Work is in progress on myasthenia gravis, the usefulness of ACTH and other drugs, the pros and cons of thymectomy, and other investigations related to drug therapy in these areas. Guidelines previously developed are now being used for the glaucoma study.

Cerebral vascular group completes status report

A report published during the year by NINDB's Cerebral Vascular Study Group presents the status of research on cerebral vascular disease and underscores critical problems which require further research. As a result of this report, the National Advisory Neurological Diseases and Blindness Council and the National Advisory Heart Council have established a joint Council Subcommittee to recommend a cerebral vascular research program consistent with the need.

The Subcommittee is composed of Dr. Irving S. Wright, chairman, Dr. James L. O'Leary, Dr. Clark H. Millikan and Dr. E. Cowles Andrus, with Dr. Murray Goldstein of NINDB as executive secretary. In order to expand the cerebrovascular field, the group will estimate program needs over a 5-year period, develop a realistic budget, and determine requirements for personnel and equipment. The Subcommittee also plans a conference of promising resident physicians on such matters as blood flow, microcirculatory areas, fibrolysins, thrombolytic process, and other related subjects for the purpose of stimulating their interest in the cerebrovascular projects.

Two NINDB cooperative studies in the cerebrovascular field are nearing completion.

The Institutes' Cooperative Study of Intracranial Aneurysms and Subarachnoid Hemorrhages, begun early in 1958, continues. In addition to the analysis of subarachnoid hemorrhages and aneurysms, the study may also prove helpful—through its large reservoir of clinical data—in solving the general problems of cerebrovascular disease.

NINDB's Cooperative Anticoagulant Project, begun late in 1957, has indicated that the use of anticoagulant drugs in preventing "little strokes"—in warding off the occurrence or recurrence of major attacks, and in reducing the neurological deficit that may result—is feasible but may involve definite risks and problems.

Report to be published on maternal-child care mission to U.S.S.R.

A report will be published early in 1962 on the second NINDB-sponsored mission of six American scientists to the U.S.S.R., where they surveyed progress in the field of maternal and child care.

Although the U.S. delegation found the Soviet "in the process of trying to catch up to our methods" in caring for mothers and their children, they report—

A program of child care in which every infant is followed continuously through adolescence.

A "superb" attitude toward children with neurological disorders such as mental retardation.

Available clinical care for every pregnant woman.

The mission was part of a scientific-cultural exchange between Russia and the United States. The American scientists participating were Drs. Stewart H. Clfford, Boston Lying-In Hospital; Allan C. Barnes, Johns Hopkins Medical School; Katherine Bain, Children's Bureau, DHEW; B. G. Greenberg, University of North Carolina; Edith Potter, Chicago Lying-In Hospital; and Fred S. Rosen, Children's Hospital, Boston.

A previous NINDB-sponsored medical exchange mission to Russia surveyed Soviet research activities in physiology and pharmacology of the nervous system.

Bibliographies and translated Russian documents on perinatal research prepared

A number of references and bibliographies concerned with perinatal research have been prepared by the Medical Literature Services of the Perinatal Research Branch, NINB. These include: References on the Placenta; The Role of Vitamin C in Etiology of Congenital Neurological Disorders and Perinatal Mortality (and First Supplement); References on Radiation; References on Infant Mortality and Morbidity; and References on Prematurity.

Four Russian documents concerned with research in this field have been translated. These papers pertain to mental development and higher nervous activity of the abnormal child; early ontogenesis of reflex activity in the child; and the status of Vitamin C metabolism in connection with workers exposed to tobacco dust.

A limited supply of these documents is available at NINDB to fill specific requests.

New NINDB brochures

Two new booklets have been added to the "Hope through Research" series originated in the Information Office of NINDB. "Cataract and Glaucoma—Hope through Research" is the first to handle two ailments together. Because of repeated histories of patients who delayed in seeking medical care for glaucoma, mistakenly believing that their failing vision was due to cataracts which must ripen, the two ailments are contrasted and defined, and people are urged to obtain prompt medical attention for all health problems. The booklet, PHS publication No. 793, Health Information Series No. 99, presents research as the hope for further progress in preventing blindness.

"Parkinson's Disease—Hope through Research" also appeals to the layman, and urges patients to keep in contact with their physicians throughout the duration of this ailment which can be helped by treatment but, at present, is not curable. An active program of research at the Institute and elsewhere has pervaded the diagnosis of the ailment with new hope. The booklet is PHS publication No. 811, Health Information Service No. 100.

Both pamphlets may be requested from NINDB.

NINDB guide on examination of the placenta published in national medical journal

An illustrated edition of the NINDB Collaborative Perinatal Research Project guide "Examination of the Placenta" was published in *Obstetrics and Gynecology.* Dr. Kurt Benirschke, chairman of the department of pathology at Dartmouth Medical School, prepared the guide for use to ensure the uniform collection of data on placental pathology at the 15 hospitals engaged in the Collaborative Project. Included among the illustrations in the published edition are 20 color photographs reproduced with funds made available by NINDB.

Diabetic retinopathy conference proceedings published

Proceedings of the Diabetic Retinopathy Conference held at Haddonfield, N.J., have been reported in a special issue of *Survey of Ophthalmology.* The Conference was supported by the Neurology Field Investigation Study Section, Division of Research Grants, under a chairman's grant to Dr. Irving H. Leopold of Wills Eye Hospital, Baltimore, who also edited the proceedings.

Noting that diabetic retinopathy is a "frightful complication of the prolonged life of the diabetic," Dr. Leopold arranged for a free discussion among experts in the various aspects of that complication in order to bring about a true exchange of ideas.

The discussions, as reported in the summary of the proceedings, covered such areas as the role of insulin deficiency in the production of retinal changes; electron microscopy of vascular lesions; metabolic pathways of glucose; microaneurysm; ocular pathological aspects of diabetes and the influence of diet, metabolism, hormones and pituitary function.

NINDB FILMS

Two professional training films, produced for the National Institute of Neurological Diseases and Blindness, illustrate techniques for conducting neurological examinations of the new born infant and the 1-year-old. The films were prepared as guides for the neurological examinations to be conducted within the Collaborative Project on perinatal causes of cerebral palsy, mental retardation, and other neurological disorders of infancy and childhood.

The first film, entitled "Neurological Examination of the Newborn," depicts testing methods for assessing the condition of the nervous system at birth, and presents some of the normal and abnormal responses to these tests. A second, "Neurological Examination of the One Year Old," illustrates similar techniques for use with this age group.

The 30-minute, color and sound films (16 mm.) were prepared under the direction of Dr. Richmond Paine, pediatric neurologist at Children's Hospital Medical Center, Boston. They are available on loan from the Information Office, NINDB, Bethesda, Md. Copies may also be obtained from the American Medical Association, Film Library, 535 N. Dearborn St., Chicago, Ill., and the Audio Visual Section, Communicable Disease Center, PHS, Atlanta, Ga.

GRANTS FOR CONSTRUCTION OF HEALTH RESEARCH FACILITIES

WITNESSES

DR. FRANCIS L. SCHMEHL, CHIEF, HEALTH RESEARCH FACILITIES, NATIONAL INSTITUTES OF HEALTH

DR. JAMES A. SHANNON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

Program and financing

[In thousands of dollars]

	1961 actual	1962 estimate	1963 estimate
Program by activities: Grants for construction and equipment (total program costs—obligations) (object class 41)	29,985	30,016	50,000
Financing:			
Unobligated balance brought forward	−1	−16	
Unobligated balance carried forward	16		
New obligational authority (appropriation)	30,000	30,000	50,000

Mr. Fogarty. Next we have "Grants for construction of health research facilities." Dr. Schmehl, do you have a statement?

General Statement

Dr. Schmehl. I have a formal statement and, with your permission, I will read from a summary.

Mr. Fogarty. Very well.

(Dr. Schmehl's prepared statement follows:)

Statement by Chief, Health Research Facilities Branch, Division of Research Grants

Mr. Chairman and members of the committee, a request in the amount of $50 million is submitted under this appropriation for 1963. This program, now in its sixth year, was authorized under Public Law 84–835, which added title VII to the Public Health Service Act. It provides for Federal assistance in the construction and/or equipping of facilities for research in the sciences related to health. This act was extended for an additional 3-year period (Public Law 85–777) in August 1958, and again for a 1-year period (Public Law 87–395) in October 1961. The latest extension also included an increase in the authorization to $50 million, together with modifications in the language, principally to expand the term "research facilities" to include research and related purposes (including research training).

The grants awarded under this authorization and paid from this appropriation are made to non-Federal public and private nonprofit institutions, competent to conduct the type of health-related research for which the facility is to be constructed, following assurances that the proposed facility will be used for health-related research for at least 10 years. All grants are on a matching basis, with the Federal share not to exceed 50 percent of the costs of the research facility portion of the projected construction. The awards are made by the Surgeon General only after the applications have previously been recommended for approval by the National Advisory Council on Health Research Facilities.

The Congress has made appropriations of $180 million for the research facilities construction program during the first 6 years of the program (1957 through 1962).

As required by title VII, annual reports have been submitted to the President and transmitted to the Congress.

GRANTS AWARDED

There has been a great and continuing demand for funds under this program ever since its inception in July, 1956. Up to the present time some $385,629,998 in Federal funds have been requested by eligible applicants. The applications for these grants have been given careful review, initially by the staff of the Health Research Facilities Branch, and then by the National Advisory Council. In the majority of instances there has been a project site visit by Council members and staff. A total of 872 grants to 336 institutions in 48 States, the District of Columbia, and Puerto Rico, in an amount of $179,998,655 has been granted from the $180 million appropriated during the first 6 years.

The distribution of the grants awarded to date has been as follows: research facilities in medical schools, $100,397,712; in dental schools, $2,153,035; in schools of osteopathy, $112,569; in schools of public health, $3,915,299. In the health-related areas of other schools, such as those for pharmacy, veterinary medicine, chemistry, and the biological sciences, these grants amount to $37,199,461 and an additional $36,220,579 has been allocated to public and private institutions, other than schools, which are engaged in health-related research. In the program to date, the allocation has been 46 percent to non-Federal public institutions and 54 percent to private nonprofit institutions.

CONTINUED DEMAND

At the present time, there are some 172 applications on hand totaling $44,965,739 recommended for approval by the Council, for which funds are not now available. Each of these requests represents a need for a facility, many of which could be started within a few weeks after the award of the grant. In a great many cases the matching funds are available and the construction plans (including the necessary working drawings), are well advanced.

CONSTRUCTION PROGRESS

In the meantime, some 70 new and deferred applications, in which $48,464,837 are requested, are awaiting review at the forthcoming April Council meeting, and additional requests will be received prior to June 30, 1962.

The completion and utilization of new and remodeled facilities, so noticeable during the previous year, has continued during the current one. As of December 15, 1961, there was a total of 331 completed projects which represented a Federal investment of $50,940,194. This is a 34.1-percent increase over the previous year with respect to dollar value, and a 25.6-percent increase with respect to projects finished.

In addition to these completed projects, there are some additional 147 projects under contract, many of these nearing completion, and an additional 68 projects for which final contract commitments have not been made. Supplementary grants, for movable equipment in these research facilities, are not included in these totals.

PROGRAM FACTORS

The past year has seen the introduction of several new factors which will have an influence on this program during the coming years. One of these is the need for new facilities for the general clinical research centers. Although many of the institutions which have participated in the initial grants for clinical centers have been able to provide the facilities for such centers by remodeling existing space, during the past year the point was reached where is was necessary to provide grants for new facilities if additional institutions were to have such clinical centers. Although there have been only five grants, totaling $1,241,255 to date for this purpose, it is expected that there will be a steady demand for such facilities during the next few years.

Another factor relates to the circumstance that Federal support for medical research and research training has undergone a major transformation during the past 6 years whereas the support for research facilities construction has remained at a constant level. As a consequence, the eightfold increase in funds for grants and training has been reflected in a greatly increased demand for facilities—a demand which it has not been possible to meet within the limits of the previous program authorization. It is our belief that the increased authorization, together with the broadened language of the title, will permit at least a partial closing of this gap.

CURRENT STATUS

An indication of the present status of the program can be obtained from a study of the program demand, as shown by the following figures as of December 31, 1961:

	Funds requested	Funds approved
1. Approved projects recommended by Council and awaiting payment	$58,953,024	$44,965,739
2. (*a*) Pending: New and deferred applications awaiting Council action (70)	48,464,837	
(*b*) Anticipated approvals, based on 65 percent approval rate		31,502,144
3. Intentions to submit applications:		
(*a*) On file, 85 requests	32,466,293	
(*b*) Anticipated approvals, based on 30 percent combined submission and approval rate		9,739,888
Totals	139,884,154	86,207,771

LEGISLATIVE AUTHORITY

Dr. SCHMEHL. Title VII of the Public Health Service Act, which authorizes grants to help construct health research facilities, was extended for 1 year in October 1961, with an increase in the authorization from $30 to $50 million, and a broadening of the term "research facilities" to include facilities for research training. Grants are made on a matching basis, with the Federal share limited to 50 percent of the research portion of the project.

PROJECTS APPROVED FOR ASSISTANCE

The Congress has made appropriations of $180 million for the program during its first 6 years. A total of 872 grants to 337 institutions in 48 States, the District of Columbia, and Puerto Rico have been awarded.

Mr. FOGARTY. Will you put a list of those in the record at this point.

Dr. SCHMEHL. They do appear in the annual report of the program being submitted to the Congress, and in the past that has always been included——

Mr. FOGARTY. Put it in here in your statement.

Dr. SCHMEHL. Yes, sir.

(The information follows:)

Approved grants under health research facilities program, title VII [1] through Dec. 31, 1961

Applicant	Type of institution	Discipline	Request	Award, fiscal year	
				1957–1959	1960-1962
Hartford Hospital, Hartford, Conn	Hospital	Medical-clinical research	$80, 558	$73, 305	$6, 886
Do	do	do	29, 397		19, 098
St. Francis Hospital, Hartford, Conn	do	Cardiovascular research	49, 260	34, 079	
University of Connecticut, Storrs, Conn	University	Pharmacy	377, 798	167, 136	
Do	do	Life sciences research	1, 000, 658	650, 000	
Yale University, New Haven, Conn. (Facility at Bethany)	Medical School	Animal pathology	42, 200		42, 200
Yale University, New Haven, Conn	University	Biophysics	300, 000	150, 000	
Yale University School of Medicine, New Haven, Conn	Medical School	Anatomy and biochemistry	517, 850	500, 000	
Do	do	Microbiology	80, 000		80, 000
Do	do	Medicine and pediatrics	285, 415	276, 153	
Do	do	Pathology	93, 200		81, 676
Do	do	Metabolic research	25, 000		25, 000
Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine	Research laboratory	Radiobiology research	25, 705	25, 058	
Do	do	Animal health research facilities	58, 203	37, 210	10, 443
University of Maine, Orono, Maine	University	Natural products research	9, 628	9, 410	
Do	do	Animal pathology	29, 135		25, 506
Do	do	do	6, 500		6, 500
Amherst College, Amherst, Mass	College	Microbiology and chemistry	160, 050	143, 064	
Austen Riggs Center, Inc., Stockbridge, Mass	Research institute	Psychiatric research	191, 367	191, 367	
Beth Israel Hospital, Boston, Mass	Hospital	Basic medical and clinical research	823, 825		823. 825
Boston City Hospital, Boston, Mass	do	Pathology	41, 710	29, 555	
Do	do	Clinical research	150, 000		150, 000
Boston City Hospital, Sears Surgical Laboratory, Boston, Mass	Research laboratory	Cellular and tissue metabolism	258, 443	100, 000	
Boston City Hospital, Thorndike Memorial Laboratory, Boston, Mass.	do	Medical-clinical research	225, 000	225, 000	
Boston Dispensary, Boston, Mass	Hospital	Rehabilitation and geriatrics	150, 000	133, 356	
Boston Lying-in Hospital, Boston, Mass	do	Obstetric research	327, 867	198, 650	
Boston University School of Medicine, Boston, Mass	Medical School	Medical and basic science research	1, 500, 000	1, 500, 000	
Boston University, Boston, Mass	University	Biological research	150, 466		76, 967
Brandeis University, Waltham, Mass	do	Biochemistry	387, 500	363, 373	
Do	do	do	349, 579		349, 579
Children's Cancer Research Foundation, Boston, Mass	Research Foundation	Cancer and basic research	612, 752	400, 000	
Children's Hospital, Boston, Mass	Hospital	Surgical research	156, 017	142, 217	
Clark University, Worcester, Mass	University	Psychology	37, 822	33, 338	
Do	do	Biological research	84, 598		84, 598
Forsyth Dental Infirmary for Children, Boston, Mass	Infirmary	Dental research	156, 260	132, 567	
Harvard University, Boston, Mass	Medical school	Physiology	201, 155		193. 329
Do	do	Anatomy and pharmacology	1, 412, 597		1, 131, 225
Harvard University (Cambridge, Mass.)	University	Basic science research	940, 400	904, 218	
Do	do	Behavioral sciences	161, 131		161, 131
Harvard University Medical School, Boston, Mass	Medical school	Anatomy and pharmacology	1, 110, 900	1, 081, 377	
Harvard University School of Public Health, Boston, Mass	School of public health	Nutrition and environmental hygiene	2, 123, 966		1, 722, 653
Holy Ghost Hospital, Cambridge, Mass	Hospital	Cancer research	143, 049	72, 271	
Marine Biology Laboratory, Woods Hole, Mass	Research laboratory	Basic and biological sciences	738, 500	369, 250	

Massachusetts Eye and Ear Infirmary, Boston, Mass	Hospital	Ophthalmology	45, 050	35, 745	
Massachusetts General Hospital, Boston, Mass	do	Neurosurgery	244, 850	95, 938	
Do	do	Psychiatry	106, 503	93, 069	
Do	do	Basic neurological research	157, 345	140, 545	5, 775
Do	do	Allergy	28, 350	20, 112	
Do	do	Orthopedic research	218, 804	107, 370	
Do	do	Neurological research	396, 927		365, 616
Do	do	Hematology research	43, 470	37, 502	
Do	do	Thyroid research	45, 664	45, 664	
Massachusetts Institute of Technology, Cambridge, Mass	University	Biology	110, 050		100, 633
Do	do	Psychology	252, 690		252, 690
Medfield Foundation, Inc., Medfield, Mass	Research Foundation	Mental Health	15, 732		15, 732
Memorial Hospital, Worcester, Mass	Hospital	Clinical research	128, 785	56, 306	58, 291
New England Center Hospital, Boston, Mass	do	Medical research	775, 282	438, 643	
New England Deaconess Hospital, Boston, Mass	do	Cancer research	135, 000	120, 000	
Red Acre Farm, Stow, Mass	Research laboratory	Biological research	23, 076	23, 076	
Retina Foundation, Boston, Mass	Research foundation	Eye research	874, 652	300, 000	392, 654
Robert B. Brigham Hospital, Boston, Mass	Hospital	Research in rheumatic diseases	11, 159	7, 525	
Tufts University School of Medicine, Boston, Mass	Medical school	Biochemistry and nutrition	25, 160	22, 448	
Do	do	Pharmacology	30, 687	23, 740	
Do	do	Basic science research	677, 000		677, 000
Tufts University, Boston, Mass	University	Sanitary engineering	5, 081		5, 081
University of Massachusetts, Amherst, Mass	do	Psychology	209, 370	176, 656	
Do	do	Zoology	375, 800	240, 304	
Do	do	Biochemistry	22, 600	4, 375	
Do	do	Bacteriology and zoology	677, 557		132, 212
Do	do	Animal pathology	9, 500		9, 500
Worcester Foundation for Experimental Biology, Shrewsbury, Mass.	Research foundation	Biology	433, 270	358, 710	
Dartmouth Medical School, Hanover, N.H	Medical school	Medical sciences research	1, 060, 025	1, 010, 324	
Dartmouth College, Hanover, N.H	College	Psychology	24, 272		24, 272
University of New Hampshire, Durham, N.H	University	Life sciences research	252, 170	150, 000	
Do	do	Microbiology	17, 125		17, 125
Fairleigh Dickinson University, Teaneck, N.J	Dental school	Dental research	32, 500	32, 458	
New Jersey State Department of Health, Trenton, N.J	State institution	Public health research	206, 525		206, 525
Neward Beth Israel Hospital, Newark, N.J	Hospital	Basic medical and clinical research	13, 300	7, 600	
Princeton University, Princeton, N.J	University	Biological sciences research	1, 101, 246	570, 000	31, 481
Rutgers, the State University, New Brunswick, N.J	do	Biological research	1, 000, 000	450, 890	
Do	do	Radiation biology	124, 338		124, 338
Do	do	Chemistry and bacteriology	19, 765	19, 765	
Do	do	Entomology research	8, 425		8, 425
Do	do	Sanitary engineering	4, 079	4, 079	
Do	do	Psychology and nutrition	261, 282		177, 171
Do	do	Radiobiology	25, 000		25, 000
Do	do	Pharmacy	16, 246		15, 467
Do	do	Sanitary engineering	61, 838		48, 963
Do	do	Psychopharmacology	19, 985		19, 837
Seton Hall College of Medicine and Dentistry, Jersey City, N.J	College of medicine and dentistry.	Basic sciences research	184, 256	139, 987	
South Jersey Medical Foundation, Camden, N.J	Research foundation	Tissue culture research	24, 100	5, 000	
St. Barnabas Medical Center, Newark, N.J	Hospital	Medical research	1, 143, 916	50, 000	

See footnotes at end of table.

Approved grants under health research facilities program, title VII[1] *through Dec. 31, 1961*—Continued

Applicant	Type of institution	Discipline	Request	Award, fiscal year	
				1957–1959	1960–1962
Vineland State School, Vineland, N.J	Institute for the mentally retarded.	Mental health research	$9,972	$9,972	
Adelphi College, Garden City, N.Y	College	Psychology	14,550	10,933	
Albany Medical College of Union University, Albany, N.Y	Medical school	Medical research	50,000	45,000	
Do	do	do	1,354,728		$1,343,674
The Animal Medical Center, New York, N.Y	Research institute	Veterinary medical research	455,000		210,533
Astor Home for Children, Rhinebeck, N.Y	Institute for emotionally disturbed boys.	Mental health research	81,576		78,695
Beth-El Hospital, Brooklyn, N.Y	Hospital	Medical research	214,952		204,844
Beth Israel Hospital, New York, N.Y	do	do	353,732		184,865
Brooklyn Botanic Garden, Brooklyn, N.Y. (facility at Kitchawan, N.Y.).	Research institute	Chemical and biological research	125,500	93,446	
Buffalo Children's Hospital, Buffalo, N.Y	Hospital	Virology	57,933	57,933	
Do	do	Clinical research	30,000		30,000
Columbia University College of Physicians and Surgeons, New York, N.Y.	Medical school	Medical research	400,000	399,346	
Columbia University, New York, N.Y	University	Biophysics and physiology	32,500	32,500	
Do	Medical school and school of public health.	Medical, public health, and nutritional research.	3,754,240		3,616,740
Cornell University Medical College, New York, N.Y	Medical school	Medical science research	1,737,500	1,300,630	
Cornell University, Ithaca, N.Y	Veterinary college	Disease-free animal research	75,000	75,000	
Do	University	Radiation biology	45,000	45,000	
Do	do	Sanitary engineering	10,685	9,905	
Do	do	Microbiological research	137,500		137,500
Eastman Dental Dispensary, Rochester, N.Y	Research institute and clinic	Basic science research	8,327		5,786
Health Research, Inc., Buffalo, N.Y. (facility at West Seneca)	Research institue	Cancer and allied diseases	281,415		243,172
Hospital for Special Surgery, New York, N.Y	Hospital	Orthopedic surgery	807,634	343,281	
Human Resources Foundation, Albertson, N.Y	Research and training center	Rehabilitation research	195,748		195,748
Hospital for Joint Diseases, New York, N.Y	Hospital	Orthopedic research	755,921		644,858
Institute for the Crippled and Disabled, New York, N.Y	Rehabilitation center	Rehabilitation research	159,255		159,255
Jewish Chronic Disease Hospital, New York, N.Y	Hospital	Chronic disease research	121,055	86,468	
Jewish Hospital of Brooklyn, Brooklyn, N.Y	do	Clinical research	566,845	288,825	
Long Island Biological Association, Cold Spring Harbor, N.Y	Research insititute	Biology	70,000		70,000
Long Island University, Brooklyn, N.Y	University	do	18,505	18,505	
Do	do	Biochemical research	21,924		17,600
Long Island University (C.W. Post College) Greenvale, N.Y	College	Psychological sciences	7,225	7,225	
Do	do	do	5,900		3,515
Maimonides Hospital of Brooklyn, Brooklyn, N.Y	Hospital	Clinical research	573,491	531,292	38,500
Mary Imogene Bassett Hospital, Cooperstown, N.Y	do	do	755,376	299,187	
Do	do	Medical research	34,747		34,747
Do	do	Radiation research	20,000		20,000
Do	do	Disease-free animal research	34,963		34,963
Medical Foundation of Buffalo, Buffalo, N.Y	Research foundation	Basic medical research	32,065	12,595	

Do	do	do	209,762		180,362
Memorial Hospital for Cancer and Allied Diseases, New York, N.Y.	Hospital	Cancer and allied diseases	2,579,944		2,579,944
Millard Fillmore Hospital, Buffalo, N.Y.	do	Medical research	160,620	60,000	
Misericordia Hospital, Bronx, N.Y.	do	Medical and surgical research	156,404	40,000	
Montefiore Hospital, Bronx, N.Y.	do	Research in chronic diseases	330,728	314,541	
Mount Sinai Hospital, New York, N.Y.	do	Pathology	47,733	42,678	
Do	do	Medical research	54,250	50,551	
New York, City of (the Public Health Research Institute), New York, N.Y.	Research institute	Public health research	1,617,500		550,000
New York Medical College, Flower and Fifth Avenue Hospitals, New York, N.Y.	Medical college	Medical and clinical research	2,935,296		2,549,981
New York, State of (Department of Health), Roswell Park Memorial Institute, Buffalo, N.Y.	Research institute	Cancer and allied diseases	2,092,436	646,000	56,525
New York, State of (Department of Mental Hygiene), New York, N.Y.	do	Psychiatry	66,000	66,000	
New York, State of (Department of Mental Hygiene), Manhattan State Hospital, Ward's Island, N.Y.	Hospital	Basic research in neurochemistry	300,000		300,000
New York, State of (Department of Mental Hygiene), Rockland State Hospital, Orangeburg, N.Y.	do	Mental health	350,000	240,603	
New York University Medical Center, New York, N.Y	Medical school	Medical science research	50,000	45,060	
Do	Medical center	Basic and clinical medical research	1,655,000	1,632,680	
Do	Medical school	Clinical research	80,000	75,298	
New York University, New York, N.Y.	College of dentistry	Dental research	69,800		69,800
Rockefeller Institute for Medical Research, New York, N.Y.	Research institute	Basic medical research	2,760,885	690,000	
St. Clare's Hospital, New York, N.Y.	Hospital	Medical research	50,700	10,771	
St. John's University, Jamaica, N.Y.	University	Biology and pharmacy	172,063	135,295	
St. Joseph's Hospital, Syracuse, N.Y.	Hospital	Pathology research	7,306	7,306	
St. Luke's Hospital, New York, N.Y.	do	Clinical research	44,161	44,161	
Do	do	Surgical research	82,574		47,380
Do	do	Hematology and gastroenterology	58,063		58,063
St. Vincent's Hospital, New York, N.Y.	do	Basic medical and clinical research	1,396,973		882,410
Sloan-Kettering Institute, Rye, N.Y.	Research foundation	Cancer research	1,750,000	1,152,750	
State University of New York (Upstate Medical Center), Syracuse, N.Y.	Medical school	Medical research	1,836,105		1,836,105
State University of New York (Downstate Medical Center), Brooklyn, N.Y.	do	Clinical research	2,362,500		2,362,500
State University of New York, College of Agriculture at Cornell, Ithaca, N.Y.	College	Pesticide residue research	20,000	18,767	
Staten Island Mental Health Society, Staten Island, N.Y.	Psychiatric clinic	Mental health	34,949		27,743
Syracuse University, Syracuse, N.Y.	University	Zoology research	23,626	23,626	
Do	do	Biological research	319,929		316,329
Do	do	do	57,972		57,972
Do	do	Zoology	57,377		57,377
Trudeau Foundation, Saranac Lake, N.Y.	Research foundation	Pulmonary diseases	487,500		487,500
University of Buffalo, Buffalo, N.Y.	University	Nuclear research in medicine	250,000	250,000	
Do	Medical school	Basic science research	850,915	850,915	
Do	University	Health science	630,248	516,977	48,828
University of Rochester School of Medicine and Dentistry, Rochester, N.Y.	Medical school	Medical and dental research	251,731	248,681	
Yeshiva University, Albert Einstein College of Medicine, Bronx, N.Y.	do	Clinical and basic medical research	402,183	242,332	

See footnotes at end of table.

Approved grants under health research facilities program, title VII [1] *through Dec. 31, 1961*—Continued

Applicant	Type of institution	Discipline	Request	Award, fiscal year	
				1957–1959	1960–1962
Yeshiva University, Albert Einstein College of Medicine, Bronx, N.Y.	do	Medical research	$3,638,819		$1,735,331
Yeshiva University, New York, N.Y.	University	Biological and chemical research	86,150	$50,000	
Albert Einstein Medical Center, Philadelphia, Pa	Medical center	Medical-clinical research	328,900	300,459	
Bryn Mawr College, Bryn Mawr, Pa	College	Biology research	339,781	314,157	
Children's Hospital of Philadelphia, Philadelphia, Pa	Hospital	Pediatric research	8,164		7,369
Children's Hospital of Pittsburgh, Pittsburgh, Pa	do	do	104,634	20,171	
Donald Guthrie Foundation, Sayre, Pa	Research foundation	Medical research	10,000	8,176	
Eastern Pennsylvania Psychiatric Institute, Philadelphia, Pa	Research institute	Psychiatry	84,599		84,599
Elizabeth Steele Magee Hospital, Pittsburgh, Pa	Hospital	Obstetrics, gynecology and pediatrics	564,768	200,000	10,246
Elwyn Training School, Elwyn, Pa	Institute for the mentally retarded.	Mental health	44,000	25,000	
Eye and Ear Hospital of Pittsburgh, Pittsburgh, Pa	Hospital	Eye and ear research	295,906		108,767
Hahnemann Medical College and Hospital, Philadelphia, Pa	Medical college	Clinical research	1,106,912		1,094,194
Home for Jewish Aged, Philadelphia, Pa	Institute for the aged	Geriatrics research	9,488	6,750	
Jefferson Medical College of Philadelphia, Philadelphia, Pa	Medical school	Biochemistry	30,755	30,749	
Do	do	Psychiatry	22,235	22,235	
Do	do	Surgery	51,883	51,883	
Do	do	Blood and plasma fractionation	24,572	24,572	
LaSalle College, Philadelphia, Pa	College	Health sciences	13,815	10,974	
Moore School of Electrical Engineering, Philadelphia, Pa	Engineering school	Electromedical research	58,000	58,000	
Pennsylvania State University, University Park, Pa	University	Sanitary engineering	9,908		9,908
Pennsylvania State Department of Health (Henry R. Landis State Hospital), Philadelphia, Pa.	State hospital	Medical and clinical research	259,490		110,915
Philadelphia General Hospital, Philadelphia, Pa	Hospital	Cardiovascular research	50,000		50,000
Philadelphia Psychiatric Hospital, Philadelphia, Pa	do	Mental health	46,281		45,114
Presbyterian Hospital, Philadelphia, Pa	do	Medical science research	413,250		255,727
St. Christopher's Hospital, Philadelphia, Pa	do	Pediatric research	23,348		23,348
Swarthmore College, Swarthmore, Pa	College	Biology	81,000		81,000
Temple University School of Medicine, Philadelphia, Pa	Medical school	Medical research	2,157,500		1,437,750
University of Pennsylvania, Philadelphia, Pa	do	Pharmacology	85,879	81,585	
Do	do	Radiological research	325,621	212,254	
Do	do	Medical research	2,181,891	1,600,000	130,095
Do	School of dentistry	Dental research	155,350	146,109	
Do	University	Biology	473,375	473,375	
Do	Medical school	Dermatology	79,824		79,824
Do	Graduate school of medicine	Basic and clinical research	124,600	100,000	24,600
Do	Medical school	Environmental research	29,629	29,629	
University of Pittsburgh, Pittsburgh, Pa	School of public health	Public health research	180,000	82,920	
Do	Schools of the health professions.	Basic medical research	686,812	600,368	
Do	do	Rheumatological and orthopedic research.	82,523		78,768

Do	Medical school	Physiology	68,000		68,000
Do	University	Life sciences	57,456	57,456	
Wills Eye Hospital, Philadelphia, Pa	Hospital	Ophthalmology	100,000	94,700	
Wistar Institute of Anatomy and Biology, Philadelphia, Pa	Research institute	Basic biological research	205,974	205,974	
Women's Medical College of Philadelphia, Philadelphia, Pa	Medical school	Medical research	948,658	546,038	
The Woods School, Langhorne, Pa	Research center	Child study and research	182,315	176,250	
Zoological Society of Philadelphia (Penrose Research Laboratory), Philadelphia, Pa.	Research laboratory	Pathology	32,600		32,600
Brown University, Providence, R.I	University	Psychology research	433,557	430,015	
Do	do	Biology	26,384	26,083	
Do	do	do	565,070		522,900
Providence College, Providence, R.I	College	Basic medical research	122,736		122,736
Rhode Island Hospital, Providence, R.I	Hospital	Cancer research	162,643	25,000	
Do	do	do	116,795		110,627
University of Rhode Island, Kingston, R.I	University	Biology	14,000		13,876
Do	do	Pharmacy	856,599		269,050
Do	do	Sanitary engineering	74,828		74,828
DeGoesbriand Memorial Hospital, Burlington, Vt	Hospital	Physiology and cardiovascular research	157,000	96,475	
University of Vermont, Burlington, Vt	Medical school	Medical and clinical research	619,000	495,639	
Do	University	Psychology	6,000		6,000
Do	do	Pathological research	722,500		708,422
Auburn, University, Auburn, Ala	do	Research in nutrition	70,000	70,000	
Do	do	Veterinary research	224,385	224,385	
Do	do	Sanitary engineering	10,400		10,334
Do	do	Human nutrition and infant research	61,980		59,086
Do	do	Biochemistry	153,560		60,290
Southern Research Institute, Birmingham, Ala	Research institute	Medical research	250,000	250,000	
Do	do	do	250,000		150,000
University of Alabama, Birmingham, Ala	Medical school	Basic and clinical research	1,194,394	1,050,268	144,126
University of Arkansas Medical Center, Little Rock, Ark	do	Medical and clinical research	1,150,855	1,066,000	
Catholic University of America, Washington, D.C	University	Biology	684,019		216,642
Children's Hospital of the District of Columbia, Washington, D.C	Hospital	Pediatric disease research	150,000	150,000	
George Washington University, Washington, D.C	Medical school	Medical and surgical research	45,000	45,000	
Do	do	Medical research	82,500	82,500	
Do	do	do	220,261	186,806	
Do	University	Science and basic health research	1,218,425		350,000
Washington Hospital Center, Washington, D.C	Hospital	Medical and clinical research	485,950		25,000
Florida State Board of Health, Vero Beach, Fla	Research center	Medical entomology	30,367	28,867	
Florida State University, Tallahassee, Fla	University	Biological sciences	475,000		475,000
Mount Sinai Hospital of Greater Miami, Inc., Miami, Fla	Hospital	Cardiopulmonary research	217,500	40,000	
National Children's Cardiac Center, Miami, Fla	do	Basic medical and clinical research	117,500		72,877
University of Florida, Gainesville, Fla	Medical school	Medical and clinical research	642,938	540,000	
Do	University	Sanitary engineering	27,670	26,612	
Do	do	Air-pollution research	8,330	8,110	
Do	Medical school	Medical research	26,000	25,107	
Do	do	do	68,800		68,800
University of Miami, Miami, Fla	University	Entomology	9,961		6,000
University of Miami and Board of Dade County Commissioners, Miami, Fla.	Medical school	Basic medical research	1,095,577	1,070,748	
	do	Ophthalmology	85,500		80,612
University of South Florida, Tampa, Fla	University	Biological research	207,731		205,194

See footnotes at end of table.

Approved grants under health research facilities program, title VII [1] *through Dec. 31, 1961*—Continued

Applicant	Type of institution	Discipline	Request	Award, fiscal year	
				1957–1959	1960–1962
Variety Children's Hospital, Miami, Fla	Hospital	Pediatric research	116, 246	116, 246	
Emory University, Emory University, Ga	Medical school	Medical research	370, 750	354, 106	
Do	University	Biology research	100, 164	100, 164	
Georgia Institute of Technology, Atlanta, Ga	do	Radioisotope and biological research	204, 500	125, 000	
Do	do	Chemistry (natural products)	8, 500		5, 815
Do	do	Sanitary engineering	22, 250		19, 642
Do	do	Micromeritics	46, 379		46, 379
Grady Memorial Hospital, Atlanta, Ga	Hospital	Clinical research	40, 967		20, 484
Medical College of Georgia, Eugene Talmadge Memorial Hospital, Augusta, Ga.	Medical school and hospital	do	835, 011	787, 460	
Piedmont Hospital, Atlanta, Ga	Hospital	Basic and clinical research	97, 220		79, 646
University of Georgia, Athens, Ga	University	Biological sciences	631, 037	631, 037	
Do	do	Pharmacy	266, 344	100, 000	
Kentucky State Department of Health, Frankfort, Ky	Health department	Public health	376, 255	100, 000	
Memorial Medical Center of Miner's Memorial Hospital Association, South Williamson, Ky.	Hospital	Medical research	60, 000	33, 210	
University of Kentucky, Lexington, Ky	Medical school	Basic medical sciences	1, 407, 342	1, 387, 539	
Do	Dental school	Dental research	757, 533		645, 827
University of Kentucky (Research Foundation), Lexington, Ky	University	Sanitary engineering	5, 620		3, 000
University of Louisville, Louisville, Ky	do	Chemistry	50, 000	50, 000	
Do	Medical and dental schools	Basic and clinical research	1, 536, 645	1, 293, 010	180, 085
American Type Culture Collection, Rockville, Md	Research institute	Microbiological culture research	98, 858		90, 278
Baltimore City Hospitals, Baltimore, Md	Hospital	Medical research	115, 000	115, 000	
Church Home and Hospital, Baltimore, Md	do	do	3, 500	2, 349	
Johns Hopkins Hospital, Baltimore, Md	do	Pediatric research	842, 320		842, 320
Do	do	Otolaryngology	60, 840		54, 590
Johns Hopkins University, Baltimore, Md	Medical school	Basic medical research	1, 860, 000	1, 860, 000	
Do	do	do	181, 401		181, 401
Do	do	Biophysics research	483, 000	327, 194	22, 806
Johns Hopkins University (Homewood Campus), Baltimore, Md	University	do	275, 000	150, 000	
Johns Hopkins University, Baltimore, Md	Hygiene and public health	Radiological science	500, 000		500, 000
Johns Hopkins University (Homewood Campus), Baltimore, Md	University	Biological sciences	508, 825		403, 375
Sinai Hospital of Baltimore, Inc., Baltimore, Md	Hospital	Basic medical and clinical research	198, 207	53, 428	
University of Maryland, Baltimore, Md	Medical school	Basic medical research	853, 918		853, 918
Do	do	Clinical research	104, 787		104, 787
University of Mississippi School of Medicine and Mississippi State Building Commission, Jackson, Miss.	Medical school	Basic medical research	1, 500, 000		1, 500, 000
University of Mississippi and Mississippi State Building Commission, University, Miss.	University	Pharmacy and biology	321, 621		269, 000
University of Mississippi, Jackson, Miss	Medical school	Basic medical research	76, 250		76, 250
The Agricultural and Technical College of North Carolina, Greensboro, N.C.	Technical college	Biochemistry	88, 076		88, 076
Duke University, Durham, N.C	Medical school	Medical research	105, 000	105, 000	

Do	do	Basic medical research	287, 500	215, 000	
Do	University	Life sciences	234, 500	234, 500	
Do	Medical school	Geriatric research	522, 378	388, 000	20, 628
Do	do	Clinical research	765, 000		765, 000
University of North Carolina, Chapel Hill, N.C	do	Pathology	39, 325	39, 325	
Do	University	Pharmacy	117, 020	13, 434	36, 750
Do	Medical school	Research in basic sciences	536, 820	471, 210	65, 610
Do	School of public health	Public health research	790, 494		726, 001
Do	University	Biological research	345, 843		265, 611
University of North Carolina (State College of Agriculture & Engineering), Raleigh, N.C.	Agricultural experimental station.	Genetics	20, 000		20, 000
Do	do	Animal research	51, 315		51, 315
Do	do	Nutritional research	401, 839		200, 920
Wake Forest College, Bowman Gray School of Medicine, Winston-Salem, N.C.	Medical school	Clinical, medical sciences research	1, 212, 563	895, 332	196, 713
University of Puerto Rico School of Medicine, Rio Piedros, P.R	do	Basic medical research	68, 004		68, 004
Clemson College, Clemson, S.C	School of agriculture	Food technology and nutrition	19, 889	9, 446	
Medical College of South Carolina, Charleston, S.C	Medical school	Basic medical and clinical research	498, 283		498, 283
Baptist Memorial Hospital, Memphis, Tenn	Hospital	Cardiovascular research	56, 021	34, 326	
University of Tennessee, Memphis, Tenn	School of pharmacy	Research in pharmacy	7, 500	5, 603	
University of Tennessee and City of Memphis Hospital, Memphis, Tenn.	Medical school	Radiological research	300, 146		144, 422
University of Tennessee, Memphis, Tenn	Dental school and school of pharmacy.	Dentistry and pharmacy	642, 357		325, 000
University of Tennessee, Knoxville, Tenn	University	Clinical research	480, 714		480, 714
Vanderbilt University, Nashville, Tenn	Medical school	Medical research	215, 020	209, 601	
Do	do	do	111, 647	100, 091	
Do	do	Microbiology	32, 000	18, 100	
Do	do	Medical research	990, 000	700, 000	
Do	do	Medical and clinical research	228, 896		228, 896
Do	do	Physiology	18, 046	18, 046	
Do	University	Sanitary engineering	33, 073		21, 675
Medical College of Virginia, Richmond, Va	Medical school	Medical sciences research	170, 123	170, 123	
Do	do	Surgical research	110, 000	110, 000	
Do	do	Basic medical and surgical research	1, 633, 449		1, 633, 449
University of Virginia, Charlottesville, Va	do	Medical research	290, 776	261, 250	12, 420
Do	University	Biology-psychology	922, 250		922, 250
Virginia Fisheries Laboratory, Gloucester Point, Va	Research center	Microbiology-pathology	37, 625		27, 345
Virginia Polytechnic Institute, Blacksburg, Va	Technical college	Microbiology, biochemistry, and nutrition.	383, 600	344, 005	39, 595
Beckley Memorial Hospital of Miner's Memorial Hospital Association, Beckley, W. Va.	Hospital	Clinical research	89, 000	79, 775	
West Virginia University, Morgantown, W. Va	Medical school	Basic medical research	56, 328	54, 850	
Do	do	Basic medical sciences	437, 324	108, 904	
Do	do	Medical research	33, 064	22, 787	
Armour Research Foundation of Illinois, Institute of Technology, Chicago, Ill.	Research foundation	Research in basic sciences	327, 869	157, 000	12, 250
Chicago College of Osteopathy, Chicago, Ill	Osteopathic school	Physiology and pharmacology	5, 548		5, 469
Chicago Medical School, Chicago, Ill	Medical school	Basic medical and clinical research	1, 621, 696	1, 000, 000	121, 696
Chicago Wesley Memorial Hospital, Chicago, Ill	Hospital	Clinical research	155, 852	49, 068	
Do	do	Medical research	95, 919		89, 479

See footnotes at end of table.

Approved grants under health research facilities program, title VII[1] *through Dec. 31, 1961*—Continued

Applicant	Type of institution	Discipline	Request	Award, fiscal year	
				1957–1959	1960–1962
Children's Memorial Hospital, Chicago, Ill	do	Pediatric research	$648,937		$648,937
Evanston Hospital Association, Evanston, Ill	do	Clinical research	70,478		66,378
Hektoen Institute for Medical Research of Cook County Hospital, Chicago, Ill.	Research institute	do	250,000	$250,000	
Do	do	Basic and clinical research	1,113,944		1,113,944
Do	do	Cardiophysiology	119,845		65,856
Illinois Department of Public Welfare, Elgin, Ill	Hospital	Biochemical research in nutrition	437,041	314,982	
Illinois Department of Public Welfare, Galesburg, Ill	do	Psychiatry	260,467	131,762	
Illinois Department of Public Welfare, Chicago, Ill	Psychiatric hospital	do	292,279	36,148	
Illinois Institute of Technology, Chicago, Ill	Technical college	Biology	5,095	5,095	
LaRabida Jackson Sanitarium, Chicago, Ill	Hospital	Rheumatic fever	299,870	192,500	
Michael Reese Hospital of Chicago, Chicago, Ill	do	Clinical research	698,895	276,000	422,895
Do	do	Biological and psychiatric research	117,080		117,080
Presbyterian-St. Luke's Hospital, Chicago, Ill	do	Basic and clinical research	1,096,700	502,630	24,780
Northern Illinois University, DeKalb, Ill	University	Basic medical research	7,500		7,500
Northwestern University, Evanston, Ill	do	Bioengineering and biochemical	1,083,675		648,161
University of Chicago, Chicago, Ill	Medical school	Obstetrics and gynecology	452,956	250,000	
Do	University	Physiological psychology	28,253	25,596	
Do	Medical school	Gastroenterology research	16,500	16,500	
Do	do	Anatomy research	56,100	56,100	
Do	do	Basic medical sciences	44,500	44,500	
Do	do	Dermatology	25,500	25,500	
Do	do	Clinical research	1,128,409		1,128,409
Do	do	Chronic disease research	170,042	157,447	11,489
Do	do	Biochemical	3,732	3,732	
Do	do	Biological sciences	1,592,575		750,000
Do	University	Zoology research	104,612	94,375	
Do	do	Medical statistics	58,976		58,976
Do	do	Zoology and psychology	35,000		35,000
Do	do	Physiology	11,263		11,263
University of Illinois, Chicago, Ill	Medical school	Immunology	50,000	50,000	
Do	Dental school	Dental research	26,250	25,260	
Do	Medical school	Anatomy	2,600	1,701	
Do	do	Biochemistry	8,500	8,500	
Do	do	Allergy research	8,400	8,400	
Do	do	Medical sciences	1,346,115		1,346,115
Do	do	Medical research	1,425,000	750,000	
Do	do	Pharmacology	3,750		3,082
University of Illinois, Urbana, Ill	University	Veterinary medicine	139,937		128,100
Do	do	Anthropod-borne diseases	942,500	693,015	
Do	do	Biochemistry	89,767	89,767	
Do	do	Biophysical research	225,343	139,173	74,425
Do	do	Physiology	140,219		80,000
Do	do	Lipid metabolism and nutrition	400,000		400,000

Indiana University, Indianapolis, Ind	Medical school	Psychiatry	103, 503	103, 503	
Do	do	Medical research	109, 500	109, 500	
Do	Dental school	Dental research	161, 972	161, 972	
Indiana University, Bloomington, Ind	University	Biology	21, 346	21, 346	
Do	do	Psychological research	543, 700		543, 700
Do	do	Physiology	134, 210		126, 626
Do	do	Biochemistry and biological sciences	533, 342		344, 866
Indiana University, Indianapolis, Ind	Medical school	Biochemistry	16, 025		16, 025
Do	do	Clinical and medical research	504, 155		357, 966
Do	do	Virus research	27, 903		26, 282
New Castle State Hospital, New Castle, Ind	Psychiatric hospital	Seizure disorders	39, 433	30, 707	
Purdue University, Lafayette, Ind	University	Life sciences	548, 197	548, 197	
Do	do	Biophysical chemistry	24, 759	24, 499	
Do	do	Veterinary medicine	995, 029	300, 000	
Do	do	Physiological research	155, 400	155, 400	
Do	do	Audiology and bioacoustics	49, 027		24, 331
Do	do	Sanitary engineering	149, 898		71, 014
Do	do	Psychology and genetics	77, 224		65, 270
University of Notre Dame Du Lac, Notre Dame, Ind	University	Biochemistry	12, 731	9, 798	
Valparaiso University, Valparaiso, Ind	do	Biological research	1, 743		1, 743
Cornell College, Mount Vernon, Iowa	College	Biology	2, 799		2, 765
Iowa State University of Science and Technology, Ames, Iowa	University	Biophysics	200, 000		200, 000
Do	do	Nutrition	40, 100		28, 239
Do	do	Food sanitation and preservation	189, 500		119, 502
Do	do	Medical research	65, 000		65, 000
Luther College, Decorah, Iowa	College	Biology and chemistry	81, 219	25, 000	
State University of Iowa, Iowa City, Iowa	Medical school	Medical research	122, 208	122, 208	
Do	do	Otolaryngology	25, 000	23, 201	
Do	do	Otological histology	3, 750	3, 750	
Do	do	Basic medical and clinical research	87, 015	81, 132	
Do	University	Sanitary engineering research	12, 000	11, 916	
Do	do	Biology	10, 000	9, 949	
Do	do	do	8, 045	6, 877	
Do	do	Nutrition	30, 738	25, 967	
Do	do	Psychology	22, 415	22, 415	
Do	Psychiatric hospital	Psychiatry	264, 938		252, 045
Do	University	Pharmacy	413, 830		207, 495
Do	Medical college	Pharmacology	55, 782		42, 700
Do	do	Basic medical research	483, 500		471, 838
Hawthorn Center, Northville, Mich	Hospital	Psychiatry	75, 000		75, 000
Henry Ford Hospital, Detroit, Mich	do	Otological research	28, 600	26, 494	
Michigan State University, East Lansing, Mich	University	Biological research	325, 000	310, 000	
University of Michigan, Ann Arbor, Mich	Medical school	Mental health research	1, 143, 350	565, 166	
Do	do	Medical research	86, 500	61, 912	
Do	do	do	137, 500	52, 011	
Do	do	Tissue culture	30, 000	22, 548	
Do	do	Medical research	250, 000		206, 529
Do	School of public health	Research in public health	871, 985	746, 225	
Do	University	Cellular biology	452, 250		452, 250
Do	Medical school	Biological chemistry	36, 850	25, 825	
Do	do	Genetics	256, 800		256, 800
Do	School of pharmacy	Pharmacy	400, 000	322, 000	17, 500

See footnotes at end of table.

Approved grants under health research facilities program, title VII [1] through Dec. 31, 1961—Continued

Applicant	Type of institution	Discipline	Request	Award, fiscal year	
				1957–1959	1960–1962
Wayne State University, Detroit, Mich	University	Life sciences	$685,000	$500,000	$47,250
Do	Medical school	Environmental health research	26,497	26,497	
Augsburg College, Minneapolis, Minn	College	Organic and physical chemistry	5,500		4,804
Carleton College, Northfield, Minn	do	Biological research	118,470		18,401
Mayo Association, Rochester, Minn	Medical foundation	Medical research	258,470	208,283	
Do	do	Biometrics	244,847		108,006
Minneapolis General Hospital Research Foundation, Inc., Minneapolis, Minn.	Research foundation	Medical and surgical research	107,730	102,871	
Do	do	do	28,600		28,600
Mount Sinai Hospital, Minneapolis, Minn	Hospital	Cardiovascular research	63,227	60,694	
St. Joseph's Hospital, St. Paul, Minn	do	Cardiopulmonary research	93,312	51,559	
St. Olaf College, Northfield, Minn	College	Environmental health research	4,739		4,739
University of Minnesota: Minneapolis, Minn	Medical school	Anatomy	26,110	26,110	
Do	do	Physiology and pharmacology	1,077,630	1,077,630	
Do	do	Cardiovascular research	270,369	229,321	
Do	do	Medical research	837,065	835,800	
Do	do	Ophthalmological research	61,964	43,089	15,050
Do	do	Cancer	305,110	193,452	
Do	University	Pharmacy	87,484	76,032	11,438
University of Minnesota, St. Paul, Minn	College of veterinary medicine.	Veterinary research	434,067	300,000	29,515
Minneapolis, Minn	University	Chemistry	41,150	41,150	
Do	do	Sanitary engineering	5,000	4,977	
Austin, Minn	Hormel Research Institute	Biological research	275,356	232,140	28,002
Minneapolis, Minn	Medical school	Surgical research	16,085	15,145	
Do	do	Pediatric research	41,425		41,425
Do	University	Organic chemistry	59,399		41,819
Do	do	Biochemistry	15,125		15,125
Do	Medical school	Otolaryngological research	28,960		23,290
Do	do	Psychiatry, neurology, and pediatrics	452,453		438,071
Malcolm Bliss Mental Health Center, St. Louis, Mo	Hospital	Mental health	32,000		32,000
Menorah Medical Center, Kansas City, Mo	do	Clinical research	216,296		189,128
Midwest Research Institute, Kansas City, Mo	Research institute	Basic medical research	145,457	142,525	
St. Louis University School of Medicine, St. Louis, Mo	Medical school	Pharmacology	49,388	49,388	
Do	do	Psychiatry	62,237		62,237
University of Kansas City, Kansas City, Mo	Dental school	Dental research	49,975	25,538	
Do	University	Pharmacy	114,067		50,000
University of Missouri:					
Columbia, Mo	Medical school	Basic medical and clinical	425,000	395,225	
Rolla, Mo	University	Sanitary engineering	7,300		7,300
Washington University, St. Louis, Mo	University hospital	Medical research	77,789	70,838	
Do	Medical school and hospital	Basic medical and clinical research	811,488	743,238	68,250
Do	University	Life sciences	189,886	162,951	

Do	do	Sanitary engineering	27, 917	25, 599	
Do	Dental school	Dental research	270, 700	200, 000	
Do	University	Sanitary engineering	19, 988		19, 587
Do	Medical school	Psychiatry	179, 090		172, 516
Case Institute of Technology, Cleveland, Ohio	Technical college	Sanitary engineering	67, 328		25, 000
Children's Hospital, Cincinnati, Ohio	Hospital	Pediatric research	348, 247	325, 037	
Children's Hospital, Columbus, Ohio	do	do	875, 000	164, 250	15, 750
Cincinnati General Hospital, Cincinnati, Ohio	do	Basic medical and clinical research	157, 577		157, 577
Cleveland Clinic Foundation, Cleveland, Ohio	Research institute	Medical research	155, 981		118, 033
Cleveland Metropolitan General Hospital, Cleveland, Ohio	Hospital	Basic medical and clinical research	420, 000		364, 332
Columbus Psychiatric Institute & Hospital, Columbus, Ohio	Research institute	Psychiatry	707, 218	268, 718	31, 282
Elizabeth Gamble Deaconess Home Association, Cincinnati, Ohio	do	Medical research	206, 500	195, 025	
Do	do	do	137, 500		137, 500
Fels Research Institute, Yellow Springs, Ohio	do	Psychophysiological research	97, 912	97, 912	
Highland View Hospital, Cleveland, Ohio	Hospital	Nutrition and metabolsim	66, 054	17, 848	
Do	do	Metabolic research	70, 460		63, 775
The Jewish Hospital (May Institute for Medical Research), Cincinnati, Ohio.	Research institute	Medical and surgical research	37, 500	37, 500	
Do	do	do	38, 012		38, 012
Oberlin College, Oberlin, Ohio	College	Basic sciences research	376, 653	50, 000	27, 628
Ohio Agricultural Experiment Station, Wooster, Ohio	Experiment station	Veterinary science	90, 000		90, 000
The Ohio Rehabilitation Center, Columbus, Ohio	Rehabilitation center	Rehabilitation research	139, 800	70, 625	
Ohio State University, Columbus, Ohio	Dental school	Dental research	290, 000	290, 000	
Do	Medical school	Medical research	2, 460, 347	900, 000	233, 573
Do	University	Human physiology	12, 000		8, 850
Do	do	Vision	75, 932		75, 932
Do	do	Optometry	100, 000		32, 900
Do	do	Animal physiology	62, 608		13, 450
Do	do	Water pollution	90, 500	85, 500	5, 000
Do	College of veterinary medicine.	Veterinary pathology	350, 000	300, 000	50, 000
St. Luke's Hospital Association, Cleveland, Ohio	Hospital	Medical-clinical research	35, 000	32, 675	
St. Vincent's Hospital, Cleveland, Ohio	do	Medical-surgical research	460, 532	105, 000	108, 646
University of Cincinnati	Medical school	Environmental medicine and industrial health.	483, 490		483, 490
Do	do	Medical research	879, 436	857, 821	
Do	University	Sanitary engineering	8, 800		8, 800
Western Reserve University, Cleveland, Ohio	Medical school	Surgical research	15, 000	5, 799	
Do	do	Pathology and basic medical research	1, 216, 200	577, 495	594, 406
Western Reserve University and University Hospitals of Cleveland	do	Medical and clinical research	2, 155, 867	1, 253, 686	793, 531
Western Reserve University	University	Behavioral sciences research	10, 356	10, 051	
Do	do	Life sciences	1, 390, 656		400, 000
Central Wisconsin Colony & Training School, Madison, Wis	Research and training center in mental health.	Mental health research	467, 030		161, 260
Lawrence College, Appleton, Wis	College	Biological research	2, 200	1, 325	858
Madison General Hospital Medical & Surgical Foundation, Inc., Madison, Wis.	Research foundation	Medical research	9, 798		3, 295
Marquette University, Milwaukee, Wis	University	Biological research	822, 414	285, 980	
Do	Dental school	Dental research	37, 627	21, 268	
Do	Medical school	Medical research	118, 380	118, 380	
Do	do	do	84, 422		84, 422

See footnotes at end of table.

Approved grants under health research facilities program, title VII [1] *through Dec. 31, 1961*—Continued

Applicant	Type of institution	Discipline	Request	Award, fiscal year	
				1957–1959	1960–1962
University of Wisconsin, Madison, Wis	Medical school	Medical sciences	$1,005,000	$1,005,000	
Do	do	Mental retardation	110,000		$110,000
Do	University	Biochemical research	300,000	300,000	
Do	do	Chemistry and pharmacy	695,750	392,779	104,721
Do	do	Psychology	20,000	20,000	
Do	do	Genetics	840,000		628,225
Arizona State University, Tempe, Ariz	do	Life sciences	536,992	280,392	
St. Joseph's Hospital, Phoenix, Ariz	Hospital	Neurological research	352,064		53,635
University of Arizona, Tucson, Ariz	University	Biological research	83,900	83,900	
Do	College of agriculture	Animal pathology	7,375	7,375	
Do	do	Animal science	13,120	13,120	
Do	College of pharmacy	Pharmaceutical chemistry	13,350		8,837
Do	College of Agriculture	Nutrition research	29,000	3,059	
Do	do	Basic medical research	390,159		267,626
Do	University	Biophysics	64,000		55,250
California Institute of Technology, Pasadena, Calif	Technical college	Biological research	477,000	477,000	
Do	do	do	54,250	54,250	
Do	do	do	16,100		16,100
Do	do	Sanitary engineering	86,033		39,900
Cedars-Sinai (formerly Cedars of Lebanon Hospital) Los Angeles, Calif.	Hospital	Basic medical and clinical research	516,571		457,138
Cedars-Sinai (formerly Mt. Sinai Hospital and Clinic) Los Angeles, Calif.	do	do	598,261		216,542
Children's Hospital of East Bay, Oakland, Calif	do	Pediatrics	167,587	75,000	
Children's Hospital Society of Los Angeles, Los Angeles, Calif	do	do	131,330	103,336	8,000
City of Hope Medical Center, Duarte, Calif	do	Clinical research	742,055		112,000
College of Osteopathic Physicians & Surgeons, Los Angeles, Calif	College of osteopathy	Medical research	109,319		107,100
Highland Alameda County Hospital, Oakland, Calif	Hospital	Lipid metabolism	101,414		65,987
The Langley Porter Neuro-Psychiatric Institute San Francisco, Calif.	Psychiatric hospital	Mental health	227,820	150,000	
Mount Zion Hospital & Medical Center, San Francisco, Calif	Hospital	Basic medical and clinical research	157,500		157,500
Pacific State Hospital, Pomona, Calif	do	Mental health	512,500		512,500
Palo Alto Medical Research Foundation, Palo Alto, Calif	Research foundation	Health-related sciences	282,145	282,145	
Pasadena Foundation for Medical Research, Pasadena, Calif	do	Basic medical research	29,572	5,740	
Presbyterian Hospital & Medical Center, San Francisco, Calif	Hospital	Surgical and cardiovascular	288,340		274,200
Rancho Los Amigos Hospital, Downey, Calif	County hospital	Research in chronic diseases	304,000		304,000
Rees-Stealy Clinic Research Foundation, San Diego, Calif	Research foundation	Medical Research	5,000	5,000	
Reiss-David Clinic for Child Guidance, Los Angeles, Calif	Child guidance clinic	Psychiatry	102,292		28,213
Scripps Clinic Research Foundation, La Jolla, Calif	Research foundation	Medical research	589,915		214,050
Stanford Research Institute, Menlo Park, Calif	do	Biological research	598,024		300,000
Stanford University Medical School, Stanford, Calif	Medical school	Basic medical sciences	2,870,891	2,623,019	238,964
Do	do	Neurophysiology	117,500		117,500
Stanford University, Stanford, Calif	University	Chemistry of natural products	210,000		210,000

Do	do	Sanitary engineering	98, 290		96, 835
University of California, Los Angeles, Calif	do	Life sciences research	1, 990, 000	632, 126	
University of California	Medical school	Neurology and psychiatry	1, 625, 623	1, 230, 000	107, 625
Do	do	Pediatrics	783, 677		556, 556
University of California:					
Richmond, Calif	University	Sanitary engineering	175, 000		175, 000
San Francisco, Calif	Medical school	Medical sciences	216, 000	25, 988	
Do	do	Cardiovascular research	380, 000	251, 875	
Do	do	Radiological research	50, 000	24, 972	
Do	do	Medical and dental research	6, 467, 354		4, 208, 329
Davis, Calif	University	Bacteriology, genetics, and biochemistry	1, 087, 259		802, 062
University of Southern California, Los Angeles, Calif	Medical school	Basic medical research	899, 850	899, 850	
Do	University	Biological sciences	1, 000, 000		1, 000, 000
Colorado Foundation for Research in Tuberculosis, Denver, Colo	Research institute	Biochemical and microbial genetics	62, 938	55, 435	
Colorado State University, Fort Collins, Colo	University	Veterinary medicine	100, 000	100, 000	
Do	do	Metabolic research	111, 228		25, 470
Do	do	Sanitary engineering	239, 071		143, 500
Do	do	Veterinary medicine	31, 237		20, 683
General Rose Memorial Hospital, Denver, Colo	Hospital	Clinical research	345, 144	50, 000	
Glockner-Penrose Hospital, Colorado Springs, Colo	do	Medical research	4, 023	4, 023	
Jewish National Home for Asthmatic Children, Denver, Colo	Research institute	Asthma and allergy research	203, 952	100, 000	
National Jewish Hospital, Denver, Colo	do	Medical research (chest diseases)	669, 779	274, 943	
Do	do	do	4, 806		4, 425
University of Colorado Medical Center, Denver, Colo	Medical school	Medical research	31, 500		31, 500
Do	do	Medical and dental research; cancer research.	1, 677, 501		1, 548, 533
Do	do	Psychiatry	83, 005		72, 580
The Queen's Hospital, Honolulu, Hawaii	Hospital	Medical and clinical research	201, 353	50, 000	
University of Hawaii, Honolulu, Hawaii	University	Basic medical research	250, 000		243, 125
Idaho State College, Pocatello, Idaho	College	Pharmacy	19, 076	19, 076	
Institute of Logopedics, Inc., Wichita, Kans	Clinic and research institute	Psycho-physica communications	613, 755		53, 061
Kansas State University of Agriculture and Applied Science, Manhattan, Kans.	University	Veterinary research	47, 700	47, 700	
Do	do	Dairy and poultry research	93, 020		93, 020
Do	do	Psychology	5, 017		5, 017
Do	do	Environmental research	80, 000		80, 000
Do	do	Genetics	14, 500		14, 500
University of Kansas, Lawrence, Kans	University	Biological research	170, 103	135, 785	
Do	do	Research in environmental health	140, 632	52, 875	17, 578
Do	do	Vertebrate research	159, 036		45, 731
University of Kansas Medical Center, Kansas City, Kans	Medical school	Clinical research	50, 000	50, 000	
Do	do	Medical science research	850, 200		850, 200
Washburn University, Topeka, Kans	University	Psychology	3, 225		2, 639
Alton Ochsner Medical Foundation, New Orleans, La	Research foundation	Clinical and medical research	325, 000	200, 000	
Louisiana State University, School of Medicine, New Orleans, La	Medical school	Basic medical research	1, 500, 000		1, 474, 938
Loyola University of the South, New Orleans, La	University	Biochemical and medical technology	72, 949		50, 000
Southern University, Baton Rouge, La	do	Basic sciences research	93, 407		93, 002
Touro Infirmary, New Orleans, La	Hospital	Medical and clinical research	494. 200	75, 000	
Tulane University School of Medicine, New Orleans, La	Medical school	Medical research	2, 442, 456	2, 040, 935	
Montana State College, Bozeman, Mont	College	Biological sciences	521, 485	130, 000	178, 224
Do	do	Veterinary research	611, 524	235, 669	14, 331

See footnotes at end of table.

Approved grants under health research facilities program, title VII [1] *through Dec. 31, 1961*—Continued

Applicant	Type of institution	Discipline	Request	Award, fiscal year	
				1957–1959	1960–1962
Montana State University, Missoula, Mont	University	Health sciences	$751,143	$130,000	$103,633
Creighton University, Omaha, Nebr	Medical school	Basic medical research	619,500		617,723
University of Nebraska:					
Omaha, Nebr	do	Neuropsychiatric	200,000	199,559	
Do	do	Cancer research	818,014		754,874
Do	University hospital	Clinical research	179,935	143,337	21,350
Lincoln, Nebr	College of agriculture	Animal pathology and hygiene	58,059		58,059
University of Nevada, Reno, Nev	University	Life sciences	158,667		56,614
Lovelace Foundation, Albuquerque, N. Mex	Medical research foundation	Basic medical and clinical research	181,550	166,242	
New Mexico College of Agriculture and Mechanical Arts, University Park, N. Mex.	College	Sanitary engineering	22,500	20,675	
New Mexico Highlands University, Las Vegas, N. Mex	University	Medicinal chemistry	150,000	150,000	
University of New Mexico, Albuquerque, N. Mex	do	do	21,238	21,238	
North Dakota State University, Fargo, N. Dak	do	Pharmacy	125,417	110,000	15,417
Do	do	Biochemical research	5,575		5,575
Do	do	Bacteriology	4,794		4,794
University of North Dakota, Grand Forks, N. Dak	Medical school	Biochemical research	95,000	74,190	
Do	University	Health related chemistry	230,476		84,027
Oklahoma State University of Agriculture and Applied Science, Stillwater, Okla.	do	Chemical research	22,500	9,975	
Do	do	Life sciences research	250,000	150,000	
Panhandle Agricultural and Mechanical College, Goodwell, Okla	College	Biology	4,513	4,513	
University of Oklahoma:					
Oklahoma City, Okla	Medical school	Basic medical and clinical research	565,000	400,000	104,329
Norman, Okla	University	Life sciences research	50,000	48,225	
Good Samaritan Hospital Portland, Oreg	Hospital	Basic medical and clinical research	14,882	11,775	
Linfield Research Institute, McMinnville, Oreg	Research institute	Radiobiological research	25,000	25,000	
Oregon State University, Corvallis, Oreg	University	Life sciencces	521,941	497,569	
Providence Hospital, Portland, Oreg	Hospital	Medical and clinical research	18,138	8,870	
Reed College, Portland, Oreg	College	Biological research	133,165	133,165	
Do	do	Medicinal chemistry	47,529		47,529
University of Oregon Medical School, Portland, Oreg	Medical school	Medical science research	1,297,955		1,297,955
University of Oregon Dental School, Portland, Oreg	Dental school	Dental research	9,877	9,877	
Do	do	do	71,900		71,900
University of Oregon, Eugene, Oreg	University	Biochemistry, biology, and molecular biology.	307,666		304,941
University of Portland, Portland, Oreg	do	Basic research in psychology	120,446		62,644
State University of South Dakota, Vermillion, S. Dak	Medical school	Basic medical sciences	126,528	114,030	12,498
Agricultural and Mechanical College of Texas, College Station, Tex	College	Plant pathology and air pollution	70,612		45,000
Houston State Psychiatric Institute for Research and Training, Houston, Tex.	Research institute	Psychiatry	87,291		87,291
Rice University, Houston, Tex	University	Biology	50,000	50,000	

Southwest Foundation for Research and Education, San Antonio, Tex.	Research foundation	Basic medical sciences	772, 619	232, 773	100, 000
Texas Medical Center, Inc., Houston, Tex	Research institute	Medical sciences research	2, 849, 131		2, 849, 131
University of Houston, Houston, Tex	University	Pharmacy research	6, 754	3, 062	
Do	do	Biology research	19, 075	17, 109	
University of Texas:					
Austin, Tex	do	Biochemical research	100, 000	100, 000	
Do	do	Sanitary engineering	4, 000	2, 770	
Do	do	Zoology	94, 078		82, 100
Port Aransas, Tex	do	Research in environmental health	200, 000		104, 797
Dallas, Tex	Southwestern medical school	Medical and clinical research	1, 000, 000		1, 000, 000
Galveston, Tex	University	Basic medical research	281, 832		281, 832
Holy Cross Hospital, Salt Lake City, Utah	Hospital	Basic medical sciences	144, 555	25, 000	
University of Utah, Salt Lake City, Utah	Medical school	Medical sciences	2, 439, 166	1, 990, 000	449, 166
Utah State University, Logan, Utah	University	Animal metabolism and nutrition	26, 157	26, 157	
Do	do	Biological sciences	258, 869		258, 869
Children's Orthopedic Hospital, Seattle, Wash	Hospital	Medical research	33, 088		19, 776
Gonzaga University, Spokane, Wash	University	Basic medical research	208, 890		25, 000
Pacific Lutheran University, Tacoma, Wash	do	Biochemical research	7, 790		7, 710
Pacific Northwestern Research Foundation, Seattle, Wash	Research foundation	Medical research	280, 575		280, 575
Washington State University, Pullman, Wash	University	Air pollution	22, 332	13, 869	
Do	do	Biochemical research	29, 925	5, 637	
Do	do	Veterinary research	100, 000	91, 656	
Do	do	Biological research	18, 100	18, 100	
Do	do	Biochemistry	370, 000	205, 400	
Do	do	Biological sciences	413, 792		408, 998
Do	do	Pesticide research	131, 500		65, 000
Do	do	Sanitary engineering	71, 954		58, 657
Do	do	Veterinary science	13, 435		13, 435
University of Washington, Seattle, Wash	do	Psychology research	167, 832	167, 832	
Do	Medical school	Basic medical research	155, 000	153, 255	
Do	Dental school	Dental research	50, 000	48, 454	
Do	Medical school	Research in health sciences	425, 000	425, 000	
University of Wyoming, Laramie, Wyo	University	Veterinary research	60, 485	51, 759	
Total			235, 335, 811	87, 283, 326	92, 715, 329

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[1] Title VII of the Public Health Service Act, as amended.

CONSTRUCTION GRANT APPLICATIONS

Dr. Schmehl. There has been a great and continuing demand for funds throughout this period. At present there are 172 applications recommended for approval by the National Advisory Council on Health Research Facilities, for a total of $44,965,739, which cannot be paid from available funds. Each of these requests represents a need for a facility which in many cases could be started within a few weeks after award of a grant.

Figures on completion of facilities are now rapidly rising. As of December 15, 1961, there were 331 completed projects representing a Federal investment of $50,940,194. This is a 34.1-percent dollar increase over the previous year, and a 25.6-percent increase in projects finished. There are some 147 projects under contract, many nearing completion, and 68 projects for which final contract commitments have not yet been made.

The eightfold increase in Federal support for research and training over the past 6 years has resulted in a greatly increased demand for facilities. Also, the need for new construction for the general clinical research centers is expected to increase sharply in the next few years. It is our belief that the increased authorization, together with the broadened language of the title, will permit at least a partial closing of this gap.

PROJECTS APPROVED AND PROPOSED

Then I would like just to take from the formal statement the current status section which is in the last page of the formal statement. As mentioned earlier, we have as of December 31, 1961, approved projects recommended by the Council and awaiting payment in the amount of $44,965,739. There are pending at the current moment new and deferred applications, 70 in number, which total $48,464,837. Assuming that these will have an anticipated approval rate of 65 percent, we would expect $31,502,144 of additional projects to be recommended by the Council.

In addition, we have 85 formal requests on file for $32,466,293, and again based on the 30-percent combined submission and approval rate because we know not all formal requests are submitted, we anticipate $9,739,888 in approvals.

So we feel that we definitely have in sight for the current fiscal year 1963, $86,207,771 in projects approved and proposed to be approved by the Council.

PAST APPROPRIATIONS FOR RESEARCH CONSTRUCTION

Mr. Fogarty. You say $180 million has been appropriated?

Dr. Schmehl. That is correct.

Mr. Fogarty. Six years at $30 million each?

Dr. Schmehl. That is right. It has been at the rate of $30 million per year through 1962.

Mr. Fogarty. 1963 is $50 million. That is the legislative authorization for 1 year pending another look at the legislation. Is that the way it was passed?

Dr. Schmehl. That is correct, sir.

MATCHING

Mr. FOGARTY. The Federal Government put up $180 million in 6 years. What did private interests put up?

Dr. SCHMEHL. The total facilities cost for those years was $788,397,741. However, these are multipurpose facilities and, to the best of our knowledge, the total health-related facilities portion of those projects was $457,536,593. That is health research.

Mr. FOGARTY. That is about $2½ of private funds for each Federal dollar.

Dr. SCHMEHL. $277 million of their funds and $180 million Federal; about 1½ of their funds to 1 of Federal funds. This is for strictly health-related facilities research portions.

FINANCING APPROVED APPLICATIONS

Mr. FOGARTY. How much would it take just to finance the approvable applications carried over from 1962?

Dr. SCHMEHL. It would take $44,965,739.

Mr. FOGARTY. How many do you expect will be approved before the end of the year?

Dr. SCHMEHL. I would expect at least another $31 million. As I mentioned, these $48 million plus are pending at the moment. As a matter of fact, project site visits are being made this day and all through this month and next month, and the Council meets in April. I would estimate $31,502,000 by the 15th of April when the Council meets.

Mr. FOGARTY. So you would have many more projects on hand than you would be able to finance?

Dr. SCHMEHL. It certainly looks that way; yes, sir.

EXTENSION OF LEGISLATION

Mr. FOGARTY. The authorization expires at the end of the fiscal year 1963. What recommendations have you or the Department made to extend this legislation?

Dr. SCHMEHL. The Department has testified on S. 1072 last April and May, and before the House on H.R. 4999 in January, January 23 to 26. There were also outside witnesses. Testimony went through January 30. The Department is proposing a 3-year bill for $50 million for each year in that particular phase. This bill has three phases. It has medical teaching, facilities for new medical schools, and expansion of existing medical schools; it has medical scholarships and extension of the health research facilities for 3 years. This is part 3 of H.R. 4999.

MATCHING PROBLEMS

Mr. FOGARTY. How is the 50–50 matching turning out?

Dr. SCHMEHL. It raises quite a few problems, not only geographically but also within individual cities. Some institutions can match relatively easily on a 50–50 matching basis. Other institutions within the same city are unable to match and have not submitted. Particularly in the southeastern area there seems to be an overall failure to be able to match. Our first project for Mississippi, for example, did not come in until the fifth year of the program.

In that general area, the Council rate of approval has been higher than in any other area in the country. That is, an individual project that came in had a better chance of getting approved and paid because there was less competition. The institutions in that area did not apply as extensively as they did in the other three areas of the country. We do notice that many individual institutions and some geographical areas have varying ability.

Mr. Fogarty. Is there any difference between the southeastern part of the country and the State of Florida, for instance? I thought Florida was in pretty good shape financially.

Dr. Schmehl. Not with respect to getting money for research facilities. Both State and individual institutions, private and State, have problems there. The State institutions have been more successful in getting money for teaching portions of their schools.

Mr. Fogarty. How about Emory University in Atlanta?

Dr. Schmehl. Emory has had trouble in matching. They have matched ultimately on the projects they have had from us, but it has taken them longer on the average than it has other institutions to match.

DENTAL SCHOOLS DIFFICULTIES

Mr. Fogarty. What has been the history of the dental schools?

Dr. Schmehl. I think this is another good example. The dental schools have been relatively few in number to come into the program and have received a relatively small amount of the funds again because they have asked for a relatively small amount. Over the 6 years, their total requests have been $4,481,000.

Mr. Fogarty. What is the main reason for this; because they are not able to match?

Dr. Schmehl. Yes, sir; I believe on the individual campus the dental schools have had much more trouble in attracting money for research facilities than have some of the other disciplines such as medicine and even pharmacy, veterinary medicine, and some of the other categories.

As you go from school to school, you note that the dental institutions have trouble getting money for facilities. The presidents will admit very flatly to you they do need new dental facilities but cannot seem to attract matching money.

Mr. Fogarty. What do you think we ought to do about that?

AMENDMENTS TO PRESENT MATCHING FORMULA

Dr. Schmehl. It would be very helpful if there were some way that the present legislation could be amended to provide incentives for areas of this type.

Mr. Fogarty. How do you think it ought to be amended?

Dr. Schmehl. I feel that actually—in NIH we have considered this for some time, trying to develop a formula—I think some formula which takes into account the problems that an individual institution or discipline such as dentistry or other discipline within the institution has in attracting matching funds for health research facilities, some sort of incentive of that type built into a formula might be helpful, sir.

Mr. Fogarty. Does the present 50–50 matching favor the development of new areas or is it more or less limited to a replacement program?

Dr. Schmehl. It is hard to answer that offhand. Certainly, there have been a number of new areas, not only new buildings at existing schools but new schools have been favored also. The Council supported projects both for dental research and medical research at the new University of Kentucky, for example, at the University of Florida, the University of Miami in Florida, and also the new University of South Florida at Tampa has received a grant.

So that new institutions have been favored, and I would say new disciplines. I am thinking, for example, of a large biophysical instrumentation facility at Ames, Iowa, which was provided in part through funds through this program. Where they have had matching funds and have come in to the Council with these, these projects have been looked upon favorably. There have been a number of remodelings, too.

CANCER, HEART, MENTAL HEALTH RESEARCH CONSTRUCTION

Mr. Fogarty. We talked about dental. What about heart and cancer and mental health?

Dr. Schmehl. This program has been operated on a broad basis where a medical school or other equivalent institution has come in with its overall needs without specifying whether these are going to be used for heart research, cancer research, and so forth. So that on the whole it has been rather difficult to say X million out of the $180 million went into heart or cancer. We can, however, cite several specific examples. For example, the Sloan-Kettering Institute constructed a large cancer research facility at Rye, N.Y., in which this Council participated and has another one underway in New York City, also with a grant from the Council.

There was a grant at the Southern Research Institute at Birmingham, which is occupied almost entirely by cancer research. The Council recommended a grant of $250,000 for that building. You can pick up isolated facilities that have been used for heart and cancer research.

GRANT CEILING

Mr. Fogarty. What about the $50 million ceiling? Is that what you recommended in the beginning? Is that what NIH recommended?

Dr. Schmehl. No, sir. The general feeling at NIH—I believe Dr. Shannon would support me in this—has been that operation at a level of about $100 million a year, particularly with some sort of provision to take care of the varying needs of these institutions—in other words, some sort of built-in provision for varying matching would no doubt be about the proper operating level.

Mr. Fogarty. Is that $100 million still a good estimate?

Dr. Shannon. We believe it is, sir. Mr. Fogarty, I would like to correct something.

Mr. Fogarty. We cannot do anything about the legislation. We can make recommendations to legislative committees, but we cannot change the legislation.

Dr. SHANNON. No, sir. I would like to correct an impression that I think may be gained from Dr. Schmehl's testimony. You talked about developing new areas. The research facilities construction program has been very effective in providing adequate facilities for groups that are already established. In the specific instances Dr. Schmehl mentioned, these facilities were for the provision of resources for staff which was for the most part already at hand, to relieve crowding and to replace outmoded facilities.

I cannot help but comment on the inadequacy of this type of program for providing wholly new resources for the future or to provide wholly new resources to enable institutions to emphasize new elements in their programs that it may be desirable to undertake at any given time.

Mr. FOGARTY. Will you supply for the record a justification of the $100 million figure and how you think it should be allocated in order to meet the needs that exist?

Dr. SHANNON. Yes, we should be glad to do that. We fully appreciate that this is not primarily the problem of this committee.

(The information follows:)

The continued advancement of medical research involves not only adequate support for the conduct of substantive research activities but a balanced investment in the resources of manpower and facilities necessary for the future growth. In 1956–57, at the time the Congress was deliberating the passage of the health research facilities program, the research grants program of the NIH amounted to approximately $90 million. At that time we also were investing $30 million in the training of research manpower and the ceiling authorization proposed for the health research facilities construction program likewise was $30 million. Hence, at that time the relationship between the volume of support for research activities, the volume of investment in the training of manpower, and the sum going into the construction of facilities was as 3–1–1. As the research programs of the NIH have grown in the period of time since 1957, the relationship of the support of the funds for research and funds for research manpower have remained roughly at 3 to 1. For instance, the President's budget for fiscal 1963 proposes a total of $472 million for research grants. It also proposes a total of $146 million for training, a portion of which will be devoted to service training in the mental health field. Consequently, funds for research training still maintain the 1 to 3 relationship to the support of research, whereas the $50 million authorized for research construction is something less than one-ninth of the total funds for research support. Studied from this viewpoint, a figure from $100 to $120 million for the construction of research facilities appears necessary in order to maintain the balance among funds for the support of research, funds for research manpower, and funds for research construction.

Mr. FOGARTY. Are there any questions? If not, is there anything else you want to say?

Dr. SCHMEHL. No, sir.

Mr. FOGARTY. Thank you very much.

COMMUNICATIONS IN THE BIOMEDICAL SCIENCES

Dr. Shannon, I hope you will be able to get your report on communicating research results to the committee in time to be printed in this hearing.

Dr. SHANNON. We will do our best, sir.

(The report referred to follows:)

COMMUNICATION IN THE BIOMEDICAL SCIENCES—A REPORT BY THE NATIONAL INSTITUTES OF HEALTH, MARCH 9, 1962

THE GENERAL ORIGIN OF THE COMMUNICATION PROBLEM

The issues surrounding communications in the biomedical sciences have their origin in two distinct but little comprehended sets of circumstances. One set is essentially historical and developmental in character; the other is essentially philosophical and absolute. A brief discussion of the general nature of these two sets of circumstances is a necessary general prelude to any productive exploration of the specific problems of communications and their amelioration.

The first set of circumstances derives from the major scientific, technological, and socioeconomic changes which have occurred in the past 25 years. The Nations' investment in science and the enlargement of knowledge through research has undergone an expansion of unprecedented velocity. In medical research alone national expenditures have risen twentyfold—from $45 million in 1940 to an estimated $890 million in 1961. This tremendous increase in scientific activity has produced research findings which have resulted in many achievements in the battle against disease and ill health, and substantially enlarged the reservoir of knowledge with further potential for effective and meaningful applications. The stream of published material which has conveyed this information has undergone a parallel expansion as, indeed, have all mechanisms of communication within the scientific community. To many observers this appears to be a wholly unmanaged and completely overwhelming flood of information, defeating the very purpose of its existence.

In this same period and as a consequence of the broad and intense scientific activity there have emerged major technological innovations in the field of information handling and data processing, exemplified by but not limitd to electronic computers and associated devices whose potentialities appear at this moment to exceed our present conceptual capabilities of commanding their fullest exploitation.

These fundamental scientific and technological changes have occurred in a period of flourishing economic activity. The gross national product has risen from $100.6 billion in 1940 to a level of $521.2 billion in 1961. Per capita disposable personal income has risen 3½ times in the same period from $576 in 1940 to $1,987 in 1961. This general economic improvement has been accompanied by or engendered a sense of rising expectations that to a higher degree than ever before in the history, the needs and wants of men will be satisfied to the maximum level. In the field of health these rising expectations have been directed toward greater national effort to solve major disease and health problems and to secure the most immediate and efficient application of the knowledge derived in this process.

These are the developmental factors that have come to play upon communication in the biomedical sciences. They are real, urgent and demanding of attention. A caution is necessary, however. The very reality and urgency of these drives tend to encourage an oversimplified and uncritical view of the manner in which the problems here present can be dealt with, and a temptation to direct our efforts toward seeking solutions in the promises of new technology rather than facing the basic but often frustrating continuing issues which lie at the heart of this problem.

This brings us to the second set of considerations which bear upon the nature of the communication problems. As noted above these are philosophical in character and as such they are essentially beyond control. There circumstances relate to two simple facts:

The body of knowledge in terms of its uses is infinite. Any part of that body of knowledge can at any time be meaningful in a particular but unpredictable set of circumstances. Any process of selection from the body of knowledge for any particular purpose has as great a probability of excluding as much or more that is potentially useful for such purpose as it includes. This is the initial and intrinsic limitation upon any device, technique, or process for communication of information.

On the other hand the capability of a human being to receive, comprehend and retain, or apply information has a finite but perhaps indeterminable time-volume quotient which is at substantial variance to the time-volume flow of potentially useful information. This is the ultimate and biological limit upon the communication of information.

Between these limits lies the area of productive exploration for improvements in the communication process. Any concept or approach to communication which implicitly assumes or depends upon achieving a capability beyond these limits is manifestly a delusion.

THE AREAS OF COMMUNICATIONS AND NIH INTERESTS

It is conventional to view the general matter of communication in the biomedical sciences as consisting of three broad areas:

(*a*) Communication within the scientific community.

(*b*) Communications between the scientific community and the health practitioners.

(*c*) Communication of useful biomedical knowledge to the lay public.

These distinctions, although useful to analyze and discuss the issues, problems, and approaches to effective communications are not, in fact, as sharp and clean cut as the simple statement of them would seem to convey. In reality many of the problems and certain of the approaches to their solution are common to all three areas.

In general terms the furtherance of the programs of the National Institutes of Health involves a concern with all three aspects of communications. However, the center of interest and the major degree of responsibility for the NIH is the area of communications within the scientific community broadly conceived. Here the problem centers around the effective communication of research findings as the necessary basis for the solution of major disease and health problems and for the furtherance of knowledge. The publication process and the subsequent management of published materials in the area of the medical sciences is a substantial component of this area of communications. In such matters the National Institutes of Health, although sharing a substantial interest, defers to the major operating role of the National Library of Medicine whose preeminent concern is the published medical literature.

In respect to the dissemination of research findings to the practicing health community the NIH, with the major exception of the National Institute of Mental Health, plays only a secondary role. This area of communications falls mainly within the purview of the Bureau of State Services and to some extent the National Library of Medicine.

This division of responsibility is not an arbitrary one, but reflects the essential distinctions in the primary functional responsibilities of the several bureaus of the Service and the practical differences between the nature of the communication problems in the respective areas.

It is important to note in respect to the role and function of the NIH in the areas of communications that these activities derive from and are subordinate to its primary mission of the conduct and support of research. As such they constitute an important supplement to the basic function. The NIH does not have a statutory role in communications or the management of scientific information separate from its categorical responsibilities, nor any coordinative function in respect to other Federal agencies. The principal Federal role in scientific information and communication activities has been assigned by law to the National Science Foundation, with whose program the NIH maintains cooperative relationships.

THE ELEMENTS OF COMMUNICATION IN THE BIOMEDICAL SCIENCES

Because the term "communications" is such a broad and equivocal word a better sense of the kinds of activities encompassed in this concept as it is utilized in this discussion of "communications in the biomedical sciences," is needed. As viewed by the National Institutes of Health "communications" comprises the following basic processes or functional elements:

1. The personal interchange

Direct relationships between and amongst persons through the spoken word and correspondence under both formal or informal circumstances constitutes the fundamental and undoubtedly the most powerful, immediate, and effective means of conveying information in the scientific and professional world. The scope, variety, and volume of such activities are beyond any compact description or adequate quantification. The general forms of such relationships are, however, quite clear and distinct.

The formally arranged meetings, conferences, seminars, symposia, colloquia, and other activities of scientific, professional, and related organizations is the basic framework of the process of personal interchange amongst scientists. These assemblies, ranging from small local affairs involving 10 to 100 individuals to large international conferences, attendance at which may well exceed 10,000 persons, constitute the vital forum of the scientific community. It is in meetings of this kind that new discoveries, major findings, and new concepts are first presented and discussed, considerably in advance of the more permanent process of publication. In addition to these more formal gatherings, there are almost numberless informal meetings, lectures, discussions, arising from the continuing interplay of scientific inquiry and the exchange between laboratories and other research environments. The NIH Weekly Calendar of Events alone lists 30 to 50 of such informal meetings each week. This activity is reflective of the currency and closeness of the interchange within the scientific community.

The basic ingredient of this personal interchange process in the scientific community is the direct person-to-person communication by conversation or correspondence on an individual basis. This personal communication, frequently resulting from contacts made at formal meetings, has become a major channel for the exchange of scientific information, and more importantly for informal consultation and discussion of research problems.

In these terms, an especially noteworthy development in this area of scientific communication is the growing influence of what have been called[1] invisible colleges (in the historic sense of colleges as communities of scholars). The leading scientists in almost every field are, today, part of one or more of these informal groups whose members are spread throughout the country, and often round the world, but who are drawn together by their common professional interest. Many scientists, in fact, maintain closer professional contact with scientists hundreds or thousands of miles away (some of whom they may never have seen) than they do with the institutional colleagues with whom they lunch.

The National Institutes of Health through its many programs and activities provides extensive support for both the formal and informal aspects of this important personal interchange process as a basic means of enlarging communication in the biomedical sciences. During fiscal year 1961 the NIH made grants totaling about $2 million in partial support of almost 100 conferences, symposia and other meetings because of their research significance (appendix A). These grants ranged from $100,000 for the first international pharmacology meeting to $800 for a conference on experimental approaches in radiotherapy. In addition to grant support for conferences and meetings approximately $167,000 was spent for such formal gatherings through the intramural programs of the NIH.

Although their principal role is in the scientific evaluation of requests for grant support, the many study sections, review committees, and special advisory groups of the NIH, now numbering over 100, form a unique framework of communication in the biomedical science community. The interchange among the members of these groups who are drawn from the universities, professional schools, and research institutions of the country and represent the highest level of competence and knowledge in their respective fields, is one of the most vital and productive of the informal communication processes. In addition, as a regular part of their function as scientific evaluation groups, study sections initiate and sponsor conferences and symposia to explore a new development, discuss the state of knowledge and needed areas of research effort in a particular field or to examine in detail a specific problem.

Normally, an appropriate professional society or academic institution will be asked to organize such a conference which will usually receive NIH grant support. Extensive use of the broad relationships and capabilities of the National Research Council and the National Academy of Sciences has been made to organize and conduct meetings directed toward the assessment of the state of knowledge and needed direction of development in scientific areas important to the biomedical sciences. Frequently, a study section will itself arrange a meeting to review the status of an area for which it has grant review responsibilities. Important among such activities has been study section exploration of the long-range development of the field of biophysics, an inquiry into the role of computers in biomedical research, and examination of biomedical instrumentation potentials and an assessment of research in staphylococcus.

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[1] By Dr. Derek DeSola Price, of Yale University, whose book, "Science Since Babylon," contains a salutary, if not universally acceptable, discussion of the communications problem.

Essential to the strengthening and enlargement of this vital personal interchange process among scientists is the support of travel by medical scientists necessary for research and scientific purposes. Use of NIH grant funds for travel purposes, and particularly international travel, is very closely scrutinized in the review process and allowances are made for travel essential to the furtherance of the research activities being supported. In like manner, the essential travel needs of NIH scientists are supported. The travel quotas of the several Institutes and divisions of the NIH total $383,000 for fiscal year 1962, of which about one-quarter will be utilized for foreign travel.

The development of these fluid channels of both formal and informal personal communication in the sciences is frequently overlooked or dismissed as peripheral by those who do not participate in their immediacy, speed, and effectiveness. These methods of personal communication are perhaps the dominant factors in the rapid postwar advancement of science. They have, in the opinion of some scientists, replaced the traditional process of publication as the primary means for the initial and immediate dissemination of research findings to those portions of the scientific community to whom it is of the first and greatest significance. Thus the oft-raised cry that major research findings of great importance lie buried and unavailable in the mass of unpublished data resulting from the lag between completion of a research project and the formal publication of the results is both a considerably overdrawn and misleading assessment of the current situation. The problems of publication comprise the second element of communication in the biomedical sciences to be discussed next. However, it is important to emphasize the importance of furthering support for the various aspects of the personal interchange process in the improvement of communications.

2. *The publication of findings*

Research, whether directed toward the solution of a specific problem or constituting a fundamental inquiry which simply seeks to extend the frontiers of knowledge, is not complete until the investigator's findings are made known to those who can apply them or are added to the reservoir of knowledge upon which the further progress of science depends. The communication of research results to the scientific community is thus, and always has been, an integral part of the research process. The publication of his findings in a scientific or professional journal is a definitive, though interim objective toward which a scientist works. It is this event which makes his findings part of the general domain of human knowledge, available for specific application or as the basis for further inquiry. It also is an event from which the scientists derive some measure of personal satisfaction that is both personally meaningful to him and on which in no small measure his personal reputation and the progress of his career depends.

Scientific journals and similar publications constitute the universally recognized permanent reservoir and primary archive of scientific knowledge. The publication of a paper in such journals represents the formal process by which a scientist adds his findings to the record book of science and makes them available to the scientific community. This process of publication for now and for the foreseeable future continues to be the fundamental element underlying all scientific communication. The problems associated with this process are therefore matters which must be of first concern in advancing communication in the sciences.

The problems to be dealt with in the publication of research findings are diverse. To assure broad availability of newly developed information, prompt publication is essential. The great postwar expansion of scientific activity has gravely complicated this process. The system of scientific publication which serves the scientific community has also grown in size, complexity and diversity. The number of journals has increased substatnially not only to provide additional publication space, but to answer the needs arising from increasing specialization within the once unified discipline of natural philosophy and the areas of interdisciplinary interests to tie together related specialized disciplines. Continued enlargement of the basic system both in the numbers and specialties of journals is inescapable.

This growth presents both economic and qualitative problems. The publication of scientific papers is expensive and for the most part is unsupported by advertising revenue. The cost of starting new journals and experimenting with new forms and devices for publication is almost prohibitive. The extension of the policy of providing page cost allowances (i.e., funds to cover the cost of publishing a paper) as a part of the necessary expense associated with the conduct of a research grant will do a great deal to alleviate these economic problems. However, broader forms of direct support of scientific publications and experimentation in publication devices are needed.

The increasing volume of scientific papers for publication imposes greater responsibility upon the editorial review and selection process. An essential element in the improvement of the scientific publication system is the establishment and maintenance of high editorial standards and criteria in admitting papers for publication. This process, a responsibility of the scientific community, must be encouraged by research supporting agencies and adequately provided for in any enlargement of the publication system.

A significant concomitant of the growth in the primary scientific publication system has been the emergence into new importance of the devices of secondary publication, including abstracts, bibliographies, review papers, and indexes. Publications and materials of this character now form an integral part of the scientific communication system. These devices offer broad, rapid, and effective access to the full range of current activity in many scientific fields. The continued expansion of primary publications is constantly increasing the need for greater coverage of the primary literature through secondary publications of this type. Of particular importance are review journals and monographs which bring together the results of the work done in related aspects of a single field by many investigators, in an evaluative context reflecting the present state of knowledge in a given area.

Language barriers present a special problem in the publication field which is becoming more serious as the volume and value of work done by non-Western scientists increase and as more and more research data appear in such unfamiliar languages as Russian and Chinese. A vigorous translating program is thus becoming an essential part of the process of making published research materials readily accessible.

NIH scientists, like their colleagues in universities and other research institutions, rely primarily on the regular channels of scientific publication for bringing their work to the attention of other scientists and practitioners. Over 1,600 papers originating at NIH appear each year in progessional journals, conference reports, and proceedings or as contributions to books, and most of these are also made available to inquirers as reprints.

NIH publishes an annual Scientific Directory-Bibliography which lists the scientific papers published by its staff members during the preceding year. This document serves, incidentally, as a concise survey of the research interests of the various NIH laboratories and clinical departments as well as a directory to the professional staff concerned with particular research problems.

In addition to the impressive contributions of its staff to the national and international journals, NIH itself publishes a number of items for the information of other investigators, practitioners, and the general public. Probably the best known of these publications is the Journal of the National Cancer Institute which is one of the four leading cancer journals in the world with a wide circulation both here and abroad. Another NIH periodical carrying original scientific articles is the Cancer Chemotherapy Reports, which has a larger circulation (about 5,000) than any of the journals in the field.

The National Cancer Institute issues under contractual arrangements Cancer Chemotherapy Abstracts which encompasses the world's cancer chemotherapy literature. For a comparable purpose the National Institute of Mental Health issues Psychopharmacology Abstracts which covers literature related to the use of pharmacologic agents in the field of mental health.

Financial support for appropriate scientific publications is provided from the research project funds of the various Institutes—the dissemination of research information is regarded as an essential part of the research process and thus eligible for support from this source. During fiscal year 1961, NIH provided $743,000—an increase of 33 percent over the preceding year—in grants for the production and distribution of primary publications in addition to estimated $840,000 expended for this purpose in the intramural program. A further $3,527,000 was expended for the support of bibliographic and reference services. Grants were made, for example, to the Journal of Biophysical and Biochemical Cytology (for the publication of supplements on restricted topics), Excerpta Medica (for the preparation of abstracts on various topics including the English translation of Japanese abstracts), Journal of Experimental Pathology (to enable it to increase its size), Journal of Lipid Research (for general support), World Neurology (to permit worldwide distribution), and to the Journal of Dental Research (for the publication of certain manuscripts).

The National Heart Institute has placed particular emphasis on the support of publications and related communication activities. The first publication to be launched was the Heart Bulletin, an illustrated journal for general practitioners. Subsequently, the Council recommended sustained support (initially for 5-year periods) for three technical serials: two monthly abstract journals, Cardiovascular Diseases (from 1957) and Gerontology and Geriatrics (from 1958), and the bimonthly Journal of Lipid Research (from 1959).

The largest single effort by the National Heart Institute in this area has been support for the Cardiovascular Literature Project, which was initiated in 1953 with a commitment through 1962. This project is for the preparation of a bibliography and for coding information about the effects of drugs on the cardiovascular system. Two volumes of the resulting Index Handbook of Cardiovascular Agents are now in press.

NIH support in the area of the primary and secondary production publications and other bibliographic and reference materials is indicative of the conviction that this process is the fundamental element of the scientific communication process. Continued efforts directed toward the sound enlargement and improvement of this system are a part of every NIH program.

3. The library process

Because publications recording the accumulation of scientific knowledge constitute the permanent wealth of science, it is essential that these records be safely and permanently housed and made readily accessible to all who may have current or future need of them. No scientist or practitioner can be expected to purchase or be able to store all the journals and books which may at some time be relevant to his work. It is the traditional function of the specialized libraries to maintain a comprehensive common pool of data sources for the professional personnel they serve.

A major deficiency in the machinery available for the effective management of information in the biomedical sciences is the inadequacy of the present library system. For various reasons, mostly economic, biomedical libraries have not kept pace with the increase in the volume of relevant publications or with the growth of the scientific community whose needs they must meet. During the past 25 years the number of biologists and biochemists has more than tripled and the number of physicians has increased by 50 percent; it is estimated that in the past 7 years alone the number of professionals in medical research has more than doubled. Yet during these 25 years not more than a handful of new medical libraries has been started and the existing libraries have fallen farther and farther behind in their ability to provide the service needed by their growing and more diversified clientele. Not only must the medical libraries of today—and still more so, of tomorrow—serve a much larger number of people but they must stock a wider range of publications reflecting not only the increased number of biomedical journals but also the wider spectrum of scientific fields encompassed in present day biomedical research.

The needs to be provided for are clear:

(*a*) *The first need of medical libraries is more space.*—There is scarcely a medical library in the country which is not already overcrowded and whose physical facilities do not impose serious inconveniences on its users. The economic difficulties which most medical schools have experienced during the past several decades have not permitted them to build new library facilities with their own funds and outside construction assistance available to them (such as the program under the Health Research Facilities Construction Act) has tended to concentrate on the primary facilities for substantive research—laboratories, animal quarters, and clinical resources. A vigorous expansion program is urgently needed if these libraries are to be in a position to sustain the level of research and its application to education and service which is projected for the immediate future. To this very evident present need must be added the fact, and its implications for increased medical library facilities, that the number of scientists engaged in medical research is expected again to double by 1970.

Much of the increase in the level of biomedical research activity will, however take place not in the medical schools but in other health-related professional schools, university biology departments, and in the hospitals which, despite some notable exceptions, are now playing a relatively small part in research.

In many of the hospitals that have a research potential in terms of the capability of their staff and the availability of clinical research opportunities, the library is totally inadequate and all too frequently consists of an ill-kept and virtually random collection of journals and books. This deficiency not only militates against a productive research program but hampers patient care because a good up-to-date library should be as essential a resource for the practicing physician as it is for the research scientist.

(*b*) *The second need for medical libraries, therefore, is help in expanding and improving their collections and services.*—No Federal program is at present directed toward this problem. The purchase by an investigator of specific books and journals essential to the conduct of a grant-supported research project is, of course, a legitimate expenditure of grant funds, but the legislative authority of NIH, as administratively interpreted, does not extend to the purchase of journals and books by, or for, libraries per se even when this would in general, facilitate the research of a number of investigators and, at the same time, assist practitioners in the same community.

While the problem of making adequate library resources available to the expanding body of research scientists is great and urgent, it is, on the whole, of manageable proportions. Equally great and urgent but much more difficult is the problem of making such resources generally and easily available to all practicing physicians and other health service personnel. There are thousands of physicians throughout the country who do not have in any practical terms, access to the reservoir of published medical knowledge whatsoever. This lack has a clear impact on the ability of the physician to apply the best diagnostic and therapeutic techniques, especially when he encounters conditions outside his normal experience, and is reflected—though it is not the only cause—in the wide disparity in the quality of professional health services that can be rendered in various parts of the country. The need here is for something much more fundamental than the dissemination of current research results or even of the latest clinical findings. It in fact involves fundamental changes in the present methods and devices for providing bibliographic services and extending the library capability in support of health services. Far too many physicians lack access to an adequate source of information on what has elsewhere already been absorbed into common practice or acquired the status of established fact.

(*c*) *The third need of medical libraries is for specially trained staff.*—To be of maximum usefulness a scientific library must be operated by individuals who are not only competent librarians but who have a broad and sophisticated acquaintanceship with the substance of the scientific disciplines with which they are concerned. Only when a librarian has such knowledge is he or she able to make the library fully responsive to the scientist's or practitioner's needs. The search for information relevant to a particular problem—especially if it concerns an interdisciplinary area of science—is frequently a research project in its own right which can only be effectively undertaken by a person well versed both in bibliographic research techniques and in the distinctive approaches and terminologies of the scientific disciplines involved. The help which a really competent, intelligent, and alert librarian can give to a scientist can hardly be exaggerated. Biomedical libraries, suitably trained, are as indispensable to research and to the practice of medicine as pathologists and laboratory and X-ray technicians.

The difficulties ecountered in the removal of these limitations relate to the lack of trained personnel and the lack of operating funds for their support were such people available. Such a lack of adequate carrier opportunities will inevitably act to limit the vigorous development of library programs and services.

(*d*) *The fourth need of the libraries is for more finely focused and more sophisticated, rapid bibliographic mechanisms.*—A library, like a reference book, is no better than its index and more effective arrangements are necessary for the cross-classification and indexing of books, journal articles, and specialized monographs. There is much room for improvement in the practices of individual libraries in this regard and for the development of central bibliographic services (which are common in some other fields) using traditional methods and techniques which should be encouraged and, if necessary, supported. However, this aspect of the library process also offers opportunities for the application of new electronic technology and associated concepts and techniques which must be systematically and vigorously investigated and exploited.

To this end the NIH provided the initial support for the MEDLARS (medical literature analysis and retrieval system) project of the National Library of

Medicine which holds great promise of providing rapid systematic access to medical literature. NIH has also included in the directive to its advisory committee on computers in medical research, responsibility for exploring the possibilities of electronic information retrieval systems for the specific needs of research in the biomedical sciences. A significant array of research proposed in this area is now being considered by that group.

Although NIH activities have contributory value in dealing with the problems of libraries, the primary role in this area lies with the National Library of Medicine. The National Library is now in the process of formulating new programs to attack the needs outlined above. The NIH will endeavor to cooperate to the fullest in the development and execution of these programs.

4. The training and educational process

The ultimate instrument for communicating the results of research is the educational and training process. Research and education are the obverse and reverse of the enlarging coinage of man's knowledge. Thus, the continued incorporation of new knowledge into the educational base of the health sciences is the essential act for the further growth of knowledge and capability in this area.

There are three aspects to be considered. The first is the continued qualitative improvement of the basic professional educational process leading to the first professional degree. The second is the continuing process of professional education and training directed toward the practicing health community as a means of upgrading and updating the state of professional knowledge concerning the new and rapidly changing concepts, techniques, and therapeutic approaches emerging from the research scene. The third is the advanced training of laboratory technical investigators in the latest research concepts and techniques in the various fields of scientific endeavor.

A great deal of attention and effort has been directed toward the first and last of these aspects of the training and educational process. The second aspect; namely, the role of the educational and training process in communication between the research and practicing health community, although recognized, has been given very little emphasis. This is perhaps the most serious inadequacy in the entire communications process in the biomedical sciences.

The rapidity with which scientific knowledge is expanding in both scope and complexity is certain to render the educational base of a physician inadequate before he has progressed very far in his professional career. The processes for transmitting information on these scientific developments amongst the research community are essentially useless to the practicing physician. Raw research data—the "meat" on which the laboratory scientist thrives—is rarely directly applicable to clinical practice and usually has no significance to or is beyond the technical comprehension of the nonacademic physician. Many of the new findings which have been developed to the point of use, in actual practice involve limitations and hazards whose import can only be comprehended through an awareness of the latest concepts of physiological, biochemical, and metabolic processes.

Traditionally, physicians have relied upon a series of essentially random devices to gain information concerning new developments and concepts and for the adoption of new drugs and therapeutic approaches. Professional meetings, medical journals, specialized public health programs and, all too often, the promotional literature of the pharmaceutical industry have constituted the major mechanisms for the updating of the professional knowledge and capability of the practicing physician in the course of his career.

The present and future pace of development in the biomedical sciences renders wholly inadequate these traditional devices. The only answer which is commensurate with the scope and nature of the problem and which constitutes the most realistic step in achieving effective communication from the research community to the practicing physician is some form of a formal large-scale system of continuing professional education which is effective throughout the entire course of a practitioner's career.

The elements of this framework of continuing professional education are fourfold:

(*a*) The first involves the envelopment of the initial phases of professional education in a vigorous, inquiring, progressive scientific atmosphere which emphasizes quality of instruction, broad curriculum content, and continuing experimentation in teaching and educational techniques.

(*b*) The second element is the substantial enlargement of the continuing educational function of the professional schools which provides for the periodic return of the practitioner to the formal educational science for the necessary updating and enlarging of his knowledge and skills and for close association with a sophisticated scientific environment. This process must become the fundamental channel of communication between the scientists and the practitioner.

(*c*) The third element involves furthering the responsibility of professional organizations and certifying bodies in support of the process of continuing education by maintaining appropriate standards of professional performance and capability through a periodic review process and engaging in appropriate training and educational activities directly.

(*d*) The fourth element is the role of health agencies and programs in providing mechanisms for the conveying of specialized knowledge through demonstrations, professional and technical assistance, specialized training activities, and through an organized and coordinated system of printed materials. films and other audiovisual devices and techniques. This process is an essential complement of the more formal continuing educational process. The emphasis in such programs would be reflective of the changing urgency of major health problems, the appropriateness of public action, and the degree of development in diagnostic, therapeutic, and preventive techniques. A potentially fruitful field for experimentation and development lies in extending the technology of closed circuit television and other forms of remote access systems utilizing central repositories of data and information in support of programs in these areas.

This concept of and the structure for a major development in continuing professional education would provide the means to overcome the most serious weaknesses in the process of medical communications. It is in this area that a major national effort is needed.

NIH programs have had a profound influence upon the training and educational process. Over half of the $400 million made available for the support of research through grants in fiscal year 1962 will be awarded to research investigators located in the medical, dental, and other health professional schools of the country. This volume of research activity associated with the basic health educational process has meant that the entire undergraduate program in the health professions is, for the most part, encompassed within an active and diverse creative setting. This relationship is conducive to the most direct and effective communication from the frontiers of research to the basic educational process.

During fiscal year 1962 almost $135 million of NIH funds will be expended in direct support of fellowships, training grants and other training activities. Important components of these training programs are aimed directly at the effective communication of current research knowledge in specific fields to health practitioners. The undergraduate teaching grant programs of Heart. Cancer and Mental Health Institutes, involve the awarding of almost $2 million to schools of medicine, dentistry, and public health for the specific purpose of incorporating in the undergraduate curriculum the latest concept and findings related to these fields and to improve the teaching content and process in these areas.

A special program of the National Institute of Mental Health is specifically directed at training general practitioners of medicine in current concepts and approaches in psychiatry as a means of enabling the physician to cope more effectively with the emotional aspects of illness encountered in general practice. Over $4 million will be expended for this purpose in 1962.

In total, almost 16,000 individuals receive either full or part-time support through the fellowship and training programs of the NIH. These programs have brought into being a new scope of graduate training in the medical sciences. The magnitude and diversity of this activity have had a profound influence in the professional educational scene and constitutes one of the most significant factors in the general process of communication in the biomedical sciences. In all professional schools, teaching, research, and practice go hand in hand and are to a very large extent dependent on each other. Raising the quality and sophistication of the research and teaching element raises the quality and sophistication of practice. And the impact of a vigorous academic environment on the practice of physicians in direct contact with it quickly transfers to the entire medical community. In virtually all professions new ideas, new knowledge, and new techniques ripple out from centers at which advanced and original work is being done and the medical profession is no exception to this pattern. One of the effects of the rapidly growing research and training support programs of the NIH has been to create new centers of medical excellence in many communities throughout the country. Initially these centers have been built around existing medical schools but increasingly the overall program has been extended to hospitals not directly a part of undergraduate education but which have research programs of good potential.

A particularly effective device from this point of view is the new program for establishing and supporting clinical research centers. These centers, which must of necessity be set up in a patient-care environment, have an immediate and direct leavening effect on the host institution, the doctors who practice there, and on the colleagues with whom they share their professional experiences. These research centers are, in fact, informal demonstration centers through which physicians will come in contact with the experimental front of their profession—especially in the multicategorical centers—in a way which is far more intelligible and effective than the most lucid journal article of the most elaborate printout of computer-selected data. The practice of medicine is in large measure still an art—much more so than engineering or even architecture—and an art is better learned from participation, observation, and discussion than from the best planned exposition or formal presentation.

Another series of programs whose principal objective is bringing to bear the results of research upon the solution of specific health problems are the array of control, training, demonstration, professional and technical assistance, and training activities aimed at the improvement of State and local health services. Although the principal responsibility for programs of this type lies with the Bureau of State Services, the NIH budget for fiscal year 1962 provides almost $38 million for these activities. These funds are for support of control and professional and technical activities in the area of cancer, heart, neurological diseases, and mental health. Under current arrangements the cancer, heart, and neurology programs in this area are carried out by the Bureau of State Services, while the mental health program is administered directly by that institute. Programs of this type represent one of the most effective means to translate advancing research knowledge into sound up-to-date health services for the Nation.

NIH has also engaged in experimentation in the use of closed circuit television and related devices for improving communications and in supplementing clinical research programs conducted within the clinical center. This activity, in conjunction with the use of other audiovisual techniques, has emphasized the value of such approaches in the research and clinical area. Further experimentation is planned.

The range and magnitude of NIH activities in the training and education process constitute the most far-reaching national efforts directly related to essential aspects of the problem of medical communications. However, except in mental health, these activities have only a limited role in the continuing education of the practitioner. This would appear to be the area most needful of new effort and approaches.

PLANNING AND DEVELOPMENT DATA

The growth of biomedical research activity has also created a need for the more systematic collection and readier availability of planning and managerial information. This kind of information is becoming increasingly necessary for the effective conduct of the overall research programs.

Research administrators in the major research institutions and granting agencies have a need for data that will display in an easily assimilable manner the whole spectrum of work in progress in the biomedical sciences and that will give some measure of the relative effort going into each of the various research areas. These data are usually most conveniently presented in terms of dollars expended, though this is often not the most meaningful yardstick, especially when comparisons are to be made between fields in which the complexity of equipment and operating costs are widely disparate, as is so often the case. More precise information is usually necessary—and much more difficult to obtain—to identify gap areas, to spot overconcentration of effort, and to determine the relationship of existing or proposed projects to the total institutional or national research program in a broad discipline or disease category. An agency, such as NIH, with wide- and long-range responsibilities for the scope and direction of an important national science program must also be concerned with assessments of future professional manpower and research facilities needs which must, of course, be developed in the light of the needs and opportunities of the substantive research.

In addition to these policy-planning aspects of long-range research administration, a major Federal granting agency has special responsibilities for deploying its tax-derived resources for the most effective attainment of specific primary national objectives laid down by the Congress and the administration, for coordinating its activities with other Federal agencies so that total Federal resources may be most efficiently used, and for full accountability for the expenditure of public funds. The satisfactory discharge of these responsibilities frequently requires information which has little practical relevance to the actual conduct of research but is nonetheless important to its administration.

In discussing the administration of medical research it is, however, essential to remember that the biomedical sciences are, in a very fundamental sense, basic sciences. It is tempting to regard clinical research as applied research because it deals with the practical problems of disease rather than abstract, dehumanized biological phenomena but this is very misleading if an analogy with, say, engineering research is thereby implied. The engineer, or the applied physicist, has for a very long time been able to apply well-established, precise, and fairly comprehensive laws, principles and physical data to the solution of his problems. The physician, or the clinical scientist, on the other hand, must deal with a vast complex of unproven hypotheses, large areas of almost total ignorance, and masses of data of varying validity and, too often, of conflicting import. The advanced state of the physical sciences in terms of precision of measurement and the state of general theory—in comparison with the life services—has made it possible to set up well-organized developmental research teams to design an atomic bomb or orbit a space capsule, not only with every assurance of ultimate success but with a reasonably meaningful timetable. It is delusory to imagine that a similar procedure is yet possible to develop cures for cancer, atherosclerosis, or any of the other dread diseases on which so much promising work is being done.

The essentially exploratory nature of all of the biosciences and the necessarily empirical procedures of clinical research not only frustrate efforts to structure and direct a coordinated research plan for the solution of a specific health problem on a parallel basis to that employed in the technical development but make such a course self-defeating. In the search for an understanding of biological processes and for the basic causes and definitive treatments of disease it is less important to prevent what may seem to be duplication of effort. Several equally competent scientists may appear to have the same basis and same objective in a research venture and thus may appear to be involved in wasteful duplication. It is more likely that in this circumstance each approach is in fact different, reffective of different backgrounds and different scientific emphases. The net result is apt to be solid progress in terms of thorough exploration of the problem, diverse data, and cross verification. There is also the unpredictable but necessarily greater probability that one will experience the revealing flash of insight or the unexpected benefit of serendipity.

The philosophy which must necessarily underlie all NIH research-grant programs is that the Federal Government cannot and should not attempt to dominate the Nation's biomedical research effort but should make its support available on the basis of the scientific excellence and promise of the projects submitted to it by qualified investigators from an alert and informed community of scientists, and that the direction of research effort should, by and large, be determined by the collective judgment of the scientific community itself rather than the arbitrary decisions of scientist-administrators in the Federal service.

For program planning advice NIH relies heavily on its long-established and comprehensive framework of advisory councils, study sections, training committees, and boards of scientific counselors and special-purpose advisory groups. The membership of these bodies comprises well-informed and highly competent specialists in the fields with which they deal as well as a high proportion of leaders in the scientific community with broad and sober views of our national biomedical research needs. These groups continually assess the state of the art in the various biomedical disciplines and categorical research not only as background for their operational task of reveiwing grant-support applications but for the specific purpose of advising on the development of NIH policies in each of its program activities.

The administration of the review process is further supported by the collation of research accomplishments, the assembling of research documentation and statistical analyses conducted by the Division of Research Grants and, in respect to individual categorical programs, by the various Institutes. In this connection a particularly useful administrative service is provided by the Science Information Exchange which was started as an internal activity at NIH and, since its transformation into a national center of research project data, has continued to be heavily supported by NIH. The Exchange routinely provides up-to-date information on the grant-support already available to applicants for NIH research awards and thus enables the Study Sections to assess the applicants' further needs for funds. More detailed statistics and more refined analyses of operational data on the extramural programs are also in process of being developed by the Statistics and Analysis Section which was created for this purpose about 2 years ago. The capability of this Section to supply program administrators with appropriate administrative data is steadily growing and its functions are being expanded as its data resourecs and the need for further operating statistics increase.

PUBLIC INFORMATION

An adequate framework for communication in the biomedical sciences must also include, as an essential feature, provisions for the dissemination of information to the public. The maintenance of good health is in large part dependent on the personal practices of each individual and the improvement of health, which is the ultimate aim of medical research, therefore requires a clear public understanding of the preventive measures it can and must take. The application of diagnostic tests and early therapy similarly depend on public awareness of clinical research achievements and a full appreciation of the services that the medical profession can render. Much personal tragedy, not to mention social and economic waste, results from the fact that many people fail to take advantage of diagnostic examinations which can identify some serious diseases in their early and still vulnerable stages or to avail themselves of treatment at a time when it is likely to be most effective. Continuous and extensive publicity is clearly necessary if the expanding capabilities of modern medicine are to be fully exploited for the welfare of our citizens.

A Federal agency, expending a significant amount of tax funds for research, also has an obligation to keep the public well-informed of current progress and of the present and potential benefits to be derived from its programs. The public has repeatedly demonstrated that it is anxious that biomedical research be pursued with maximum vigor; it is clearly incumbent on Federal administrators of this research effort to acknowledge the public's confidence and support with candid and lucid reports of research achievements and of future program needs.

To these ends the NIH maintain public information programs which encompass not only direct publicity activities (such as publications and exhibits for lay audiences) but also very close cooperation with other parts of the Public Health Service dealing more directly with the public and with the voluntary health agencies.

THE PRIMARY AREAS OF ATTACK

Stepping back from the rather close examination of the major elements which comprise the process of communication in the biomedical sciences, the broad objectives toward which the major and primary effort should be directed to secure effective improvement in communications between the scientific community and the area of medical practice and health sciences emerge sharply:

1. *Achieve maximum capability for the prompt publication of research findings in the scientific and professional literature supplemented by a broad, coordinated system of secondary publication and other bibliographic devices*

A broad, capable system of primary and secondary publication forms the basic framework of scientific and professional communication. Although the specific needs of the investigator differ from those of the practitioner, their dependency upon such a system is equal. Major efforts to improve and extend the basic system and to provide effective supplementation through an integrated series of secondary publications is therefore a first order of effort. Positive steps in this direction involve:

(*a*) Acceptance by all granting agencies of the page cost requirements of scientific publication as an appropriate expense associated with the research activity being supported.

(*b*) Assistance in the support of the publication of new and expanded journals to meet the developing needs of the diverse and active scientific scene.

(*c*) Coordinated efforts to extend the present secondary publication mechanisms to provide broad and detailed coverage of the primary publication universe with special adaptations to meet the needs of health practitioners.

2. *Provide for maximum accessibility to the published literature of the biomedical sciences and the most effective means for its bibliographic management*

The center of effort in achieving this objective is the medical library system of the country. A national pattern of medical libraries, capable of subserving the growing medical research activities, the expanding academic needs, and with special programs and facilities for the practicing health community, is the sine qua non of the process of communication in the health sciences. Meeting the needs for expanded library facilities and for greatly modernized and broadened library services is therefore one of the most important tasks to be undertaken in diminishing the problem of communication in the biomedical sciences.

Actions to meet these needs must include:

(*a*) Support for the construction of new and the expansion and renovation of existing medical libraries under a national plan reflecting research, academic and service needs.

(*b*) Establishment of training programs to enlarge the numbers of trained and specialized library personnel.

(*c*) Direct support of basic library services and the acquisition of books and specialized equipment to strengthen existing and make possible the extension of library functions, particularly in the research and service areas.

(*d*) Greater investment in research and development in the processes of storage and retrieval and in applying the potentialities of the new electronic technologies to the handling of bibliographic materials and the extension of library services.

3. *Envelop the productive careers of physicians and other health practitioners in a formal process of continuing professional education shared in by the schools, professional organizations, and the health agencies*

In the final analysis, the soundest transfer of research findings to effective application in health practice takes place in an educational setting. The rapid pace of scientific advancement means that such transfer must be a continuous process. Thus a broad framework providing a purposeful and formal means for continuing professional education of physicians and other health practitioners must become the basic structure for communication between the frontier of science and the scene of practice in the health community. Under such arrangements, health practitioners can obtain sound information on new drugs, therapeutics, techniques, and scientific concepts in a context which provides adequate comprehension of the limitations and hazards involved and contributes to the enlargement and updating of their professional knowledge. This process, complemented by an adequate system of resources for management of the professional literature and supplementary adaptations of storage and retrieval mechanisms, would achieve a significant advance in health communications.

A framework of continuing professional education for the practicing health community would involve—

(*a*) The substantial enlargement of the continuing education function of the professional schools.

(*b*) A greater exercise of responsibility by professional organizations and certifying boards in assuring the continued maintenance of high professional knowledge and capability through appropriate review and participation in the continuing education process.

(*c*) Effective supplementation of the continuing education process by health agencies through demonstration, professional and technical assistance, and experimentation in the adaptation of information devices and technologies to the needs of health practitioners.

A comprehensive national effort involving official, academic, and professional bodies in developing a broad formal program of continuing professional education will provide the means to overcome the most serious weaknesses in the process of communication from the researcher to the practitioner.

It is in terms of these three broad areas of attack that the National Institutes of Health views the approach to the sound long-range development of mechanisms for effective and meaningful communications in the biomedical sciences. As has been noted throughout this report, the several programs of the NIH are making a substantial contribution to the dissemination of scientific information in their respective areas. Reflective of this effort is the fact that although NIH research expenditures amount to only 4 percent of total Federal expenditures for research and development, NIH expenditures for scientific and technical information activities are almost 10 percent of the Federal total in this area—over twice as much as its proportionate share of the total Federal research and development.[2]

However, merely facilitating the accessibility and dissemination of scientific information will be of little benefit—and may be dangerously misleading—unless it is part of a really meaningful approach to the much more serious problem of insuring that all those concerned with the preservation and restoration of health have the means to maintain the highest attainable level of professional competence and comprehension. It is to this broad end that major national efforts must be directed. Development of programs for this purpose involve many agencies beyond the NIH and the Public Health Service. But it is with this sense of the perspective of the communication problem and really meaningful approaches to its solution that the National Institutes of Health will direct its efforts within its area of responsibility.

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[2] Federal Funds for Science X, National Science Foundation.

APPENDIX A

Obligations for scientific and technical information activity

[Dollar amounts in thousands]

	Fiscal year 1960 actual					Fiscal year 1961 estimated				
	Total Federal	PHS	NIH	PHS as percent of Federal	NIH as percent of Federal	Total Federal	PHS	NIH	PHS as percent of Federal	NIH as percent of Federal
Total scientific and technical information activity	$75, 870	$9, 013	$6, 121	11. 9	8. 1	$85, 591	$11, 129	$7, 987	13. 0	9. 3
Primary production and distribution	36, 986	2, 196	1, 201	5. 9	3. 2	41, 255	2, 615	1, 583	6. 3	3. 8
Bibliographic and reference services	28, 412	4, 635	2, 954	16. 3	10. 4	31, 903	5, 424	3, 527	17. 0	11. 1
Scientific symposia and technical meetings	7, 557	1, 760	1, 580	23. 3	20. 9	8, 220	2, 336	2, 126	28. 4	25. 9
R. & D. in scientific communication and documentation	2, 915	422	386	14. 5	13. 2	4, 213	754	751	17. 9	17. 8
Total R. & D. obligations (in millions)	7, 549. 7	302. 3	274. 3	4. 0	3. 6	9, 194. 9	410. 9	374. 5	4. 5	4. 1

Source: National Science Foundation: Federal Funds for Science X (NSF 61-82; 1962).

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